PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 7 : C07D 213/02, A61K 31/44 — A1

(11) International Publication Number: **WO 00/61559**

(43) International Publication Date: 19 October 2000 (19.10.00)

(21) International Application Number: PCT/US00/09169

(22) International Filing Date: 7 April 2000 (07.04.00)

(30) Priority Data:

60/128,667	9 April 1999 (09.04.99)	US
60/151,807	31 August 1999 (31.08.99)	US

(63) Related by Continuation (CON) or Continuation-in-Part (CIP) to Earlier Applications

US	60/128,667 (CIP)
Filed on	9 April 1999 (09.04.99)
US	60/151,807 (CIP)
Filed on	31 August 1999 (31.08.99)

(71) Applicant *(for all designated States except US)*: SHIONOGI BIORESEARCH CORP. [US/US]; 45 Hartwell Street, Lexington, MA 02173 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: HUANG, Tai-Nang [US/US]; 67 Sherburne Road South, Lexington, MA 02173 (US). LIANG, Guiqing [CN/US]; Apartment 4, 62 Mill Street, Woburn, MA 01801 (US). SHEN, Ming [US/US]; 26 Bar Gate Road, Guilford, CT 06437 (US). ZHANG, Shijie [CN/US]; 137 Parlmont Park, North Billerica, MA 01862 (US).

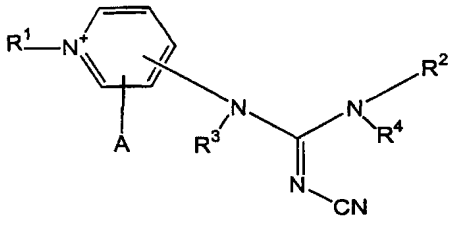
(74) Agent: TSAO, Y., Rocky; Fish & Richardson P.C., 225 Franklin Street, Boston, MA 02110-2804 (US).

(81) Designated States: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published

With international search report.

(54) Title: *N*-SUBSTITUTED CYANOGUANIDINE COMPOUNDS



(I)

(57) Abstract

N-substituted cynanoguanidine compounds of formula (I): are disclosed. N-substituted cyanoguanidine compounds of the present invention possess a high specificity for tumor cells. Also disclosed are methods for preparing such N-substituted cyanoguanidine compounds.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	**ES**	Spain	**LS**	Lesotho	**SI**	Slovenia
AM	Armenia	**FI**	Finland	**LT**	Lithuania	**SK**	Slovakia
AT	Austria	**FR**	France	**LU**	Luxembourg	**SN**	Senegal
AU	Australia	**GA**	Gabon	**LV**	Latvia	**SZ**	Swaziland
AZ	Azerbaijan	**GB**	United Kingdom	**MC**	Monaco	**TD**	Chad
BA	Bosnia and Herzegovina	**GE**	Georgia	**MD**	Republic of Moldova	**TG**	Togo
BB	Barbados	**GH**	Ghana	**MG**	Madagascar	**TJ**	Tajikistan
BE	Belgium	**GN**	Guinea	**MK**	The former Yugoslav Republic of Macedonia	**TM**	Turkmenistan
BF	Burkina Faso	**GR**	Greece			**TR**	Turkey
BG	Bulgaria	**HU**	Hungary	**ML**	Mali	**TT**	Trinidad and Tobago
BJ	Benin	**IE**	Ireland	**MN**	Mongolia	**UA**	Ukraine
BR	Brazil	**IL**	Israel	**MR**	Mauritania	**UG**	Uganda
BY	Belarus	**IS**	Iceland	**MW**	Malawi	**US**	United States of America
CA	Canada	**IT**	Italy	**MX**	Mexico	**UZ**	Uzbekistan
CF	Central African Republic	**JP**	Japan	**NE**	Niger	**VN**	Viet Nam
CG	Congo	**KE**	Kenya	**NL**	Netherlands	**YU**	Yugoslavia
CH	Switzerland	**KG**	Kyrgyzstan	**NO**	Norway	**ZW**	Zimbabwe
CI	Côte d'Ivoire	**KP**	Democratic People's Republic of Korea	**NZ**	New Zealand		
CM	Cameroon			**PL**	Poland		
CN	China	**KR**	Republic of Korea	**PT**	Portugal		
CU	Cuba	**KZ**	Kazakstan	**RO**	Romania		
CZ	Czech Republic	**LC**	Saint Lucia	**RU**	Russian Federation		
DE	Germany	**LI**	Liechtenstein	**SD**	Sudan		
DK	Denmark	**LK**	Sri Lanka	**SE**	Sweden		
EE	Estonia	**LR**	Liberia	**SG**	Singapore		

N-SUBSTITUTED CYANOGUANIDINE COMPOUNDS

CROSS-REFERENCE TO RELATED APPLICATIONS

Pursuant to 35 USC §119(e), this application claims the benefit of prior U.S. provisional applications 60/128,667, filed April 9, 1999; and 60/151,807, filed August 31, 1999.

BACKGROUND

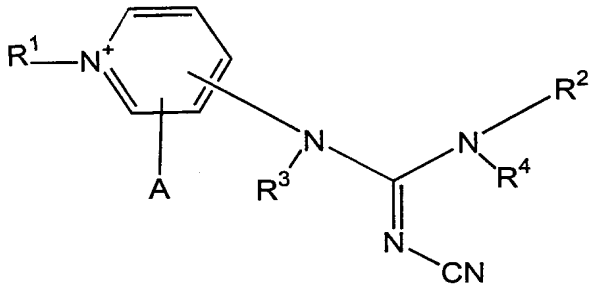
Cancer remains a formidable disease with a high mortality rate in today's society. Indeed, cancer is second only to cardiovascular disease as a cause of death, killing one out of four people in developed countries.

Cancerous tumors commonly originate from normal cells which transform into malignant cells or tumors. The initial tumor growth may be slow and thus may be difficult to detect. The growth often becomes more aggressive and invasive with time, eventually spreading throughout the whole body and resulting in death.

Cancer treatment usually includes immunotherapy, surgery, radiation, hormones, and chemotherapy. In the past forty years, cancer chemotherapy has truly revolutionized the treatment of malignant tumors. Curative treatment has been discovered for many of the cancers that affect children and young adults, including acute lymphocytic leukemia, Hodgkin's disease, testicular carcinoma, and many others. However, despite being a powerful method of treating cancer, chemotherapy does suffer from a few problems. The most prominent problem is the low specificity of the anticancer agents. That is, most anticancer agents do not adequately distinguish normal cells from cancer cells. As a result, they often carry undesirable serious side effects. Such limitations of conventional chemotherapies underscore the urgent need for new anticancer agents with high antitumor activities and specificity to the cancerous cells.

SUMMARY

An aspect of this invention relates to *N*-substituted pyridyl cyanoguanidine compounds of formula (I):



(I)

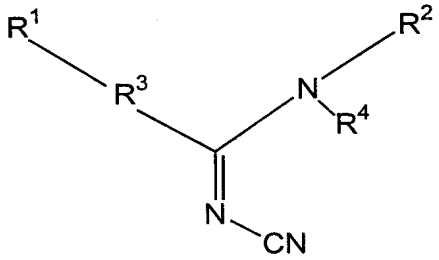
R^1 is $-X^1-Y^1-X^2-R^a-X^3-Y^2-X^4-R^b$ and R^2 is $-X^5-Y^3-X^6-R^c-X^7-Y^4-X^8-R^d$. Each of X^1, X^2, X^3, X^4, X^5, X^6, X^7, and X^8, independently, is a bond, or a C_{1-6} alkylene chain optionally containing a double bond or a triple bond and further optionally substituted with alkyl, alkenyl, alkynyl, alkoxy, hydroxyl, halo, carboxyl, amino, nitro, cyano, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, aminosulfonyl, alkylsulfonylamino, alkylcarbonyloxy, alkyloxycarbonyl, alkylcarbonyl, formyl, alkylcarbonylamino, or aminocarbonyl. Each of Y^1, Y^2, Y^3, and Y^4, independently, is a bond, -O-, -S-, -SO-, $-SO_2-$, $-N(R^x)-$, -CO-, $-N(R^x)-CO-$, $-CO-N(R^x)-$, $-N(R^x)-SO_2-$, $-SO_2-N(R^x)-$, $-N(R^x)-CO-O-$, $-O-CO-N(R^x)-$, $-N(R^x)-CO-N(R^y)-$, -O-CO-, -CO-O-, $-O-SO_2-$, or $-SO_2-O-$ where each of R^x and R^y, independently, is hydrogen, alkyl, hydroxylalkyl, amino, cyano, haloalkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, aralkyl, or heteroaralkyl. Each of R^a and R^c, independently, is a bond, or cycloalkyl, heterocycloalkyl, cycloalkenyl, heterocycloalkenyl, aryl, or heteroaryl, optionally substituted with alkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, alkoxy, hydroxyl, hydroxylalkyl, carboxyl, halo, haloalkyl, amino, aminoalkyl, nitro, cyano, aryloxy, heteroaryloxy, aralkoxy, heteroaralkoxy, alkylcarbonyloxy, alkyloxycarbonyl, arylcarbonyloxyalkyl, aryloxycarbonylalkyl, alkylcarbonyl, formyl, aminocarbonyl, alkylcarbonylamino, alkylsulfonylamino, aminosulfonyl, aminocarbonyloxy, or alkyloxycarbonylamino. Each of R^b and R^d, independently, is hydrogen or a cyclic moiety having 3-20 ring atoms, optionally substituted with alkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, alkoxy, hydroxyl, hydroxylalkyl, carboxyl, halo, haloalkyl, amino, aminoalkyl, nitro, cyano, aryloxy, heteroaryloxy, aralkoxy, heteroaralkoxy, alkylcarbonyloxy, alkyloxycarbonyl, arylcarbonyloxyalkyl, aryloxycarbonylalkyl, alkylcarbonyl, formyl, oxo, aminocarbonyl, alkylcarbonylamino, alkylsulfonylamino, aminosulfonyl, aminocarbonyloxy, or alkyloxycarbonylamino. Each of R^3 and R^4, independently, is hydrogen, alkyl, alkoxy, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, alkylcarbonyloxy, alkyloxycarbonyl, alkylcarbonyl, alkylcarbonylamino, or alkylaminocarbonyl. A is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, cycloalkenyl, heterocycloalkenyl, aryl, heteroaryl, aralkyl, heteroaralkyl, alkoxy, hydroxyl, hydroxylalkyl, thio, carboxyl, halo, haloalkyl, amino, aminoalkyl, alkylcarbonyloxy, alkyloxycarbonyl, alkylcarbonyl, alkylcarbonylamino,

aminocarbonyl, alkylsulfonylamino, aminoisulfonyl, sulfonic acid, or alkylsulfonyl. Note that neither R^1 nor R^2 is a hydrogen and at least one of R^1 and R^2 contains a cyclic moiety having 3 to 20 ring atoms or a straight chain having 4 to 24 chain atoms.

Another aspect of this invention relates to a *N*-substituted pyridyl cyanoguanidine compounds of formula (I), *supra*. R^1 is $-X^1-Y^1-X^2-R^a-X^3-Y^2-X^4-R^b$ and R^2 is $-X^5-Y^3-X^6-R^c-X^7-Y^4-X^8-R^d$. Each of X^1, X^2, X^3, X^4, X^5, X^6, X^7, and X^8, independently, is a bond, or a C_{1-6} alkylene chain optionally containing a double bond or a triple bond and further optionally substituted with alkyl, alkenyl, alkynyl, alkoxy, hydroxyl, halo, carboxyl, amino, nitro, cyano, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, aminosulfonyl, alkylsulfonylamino, alkylcarbonyloxy, alkyloxycarbonyl, alkylcarbonyl, formyl, alkylcarbonylamino, or aminocarbonyl. Each of Y^1, Y^2, Y^3, and Y^4, independently, is a bond, -O-, -S-, -SO-, $-SO_2-$, $-N(R^x)-$, -CO-, $-N(R^x)-CO-$, $-CO-N(R^x)-$, $-N(R^x)-SO_2-$, $-SO_2-N(R^x)-$, $-N(R^x)-CO-O-$, $-O-CO-N(R^x)-$, $-N(R^x)-CO-N(R^y)-$, -O-CO-, -CO-O-, $-O-SO_2-$, or $-SO_2-O-$ where each of R^x and R^y, independently, is hydrogen, alkyl, hydroxylalkyl, amino, cyano, haloalkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, aralkyl, or heteroaralkyl. Each of R^a and R^c, independently, is a bond, or cycloalkyl, heterocycloalkyl, cycloalkenyl, heterocycloalkenyl, aryl, or heteroaryl, optionally substituted with alkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, alkoxy, hydroxyl, hydroxylalkyl, carboxyl, halo, haloalkyl, amino, aminoalkyl, nitro, cyano, aryloxy, heteroaryloxy, aralkoxy, heteroaralkoxy, alkylcarbonyloxy, alkyloxycarbonyl, arylcarbonyloxyalkyl, aryloxycarbonylalkyl, alkylcarbonyl, formyl, aminocarbonyl, alkylcarbonylamino, alkylsulfonylamino, aminosulfonyl, aminocarbonyloxy, or alkyloxycarbonylamino. Each of R^b and R^d, independently, is hydrogen or a cyclic moiety having 3-20 ring atoms, optionally substituted with alkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, alkoxy, hydroxyl, hydroxylalkyl, carboxyl, halo, haloalkyl, amino, aminoalkyl, nitro, cyano, aryloxy, heteroaryloxy, aralkoxy, heteroaralkoxy, alkylcarbonyloxy, alkyloxycarbonyl, arylcarbonyloxyalkyl, aryloxycarbonylalkyl, alkylcarbonyl, formyl, oxo, aminocarbonyl, alkylcarbonylamino, alkylsulfonylamino, aminosulfonyl, aminocarbonyloxy, or alkyloxycarbonylamino. R^3 is hydrogen, alkyl, alkoxy, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, alkylcarbonyloxy, alkyloxycarbonyl, alkylcarbonyl, alkylcarbonylamino, or alkylaminocarbonyl. R^4 is a C_{1-4} alkylene chain in which the terminal carbon atom not bonded to the guanidinyl nitrogen atom is bonded to a carbon chain atom of X^5 or X^6, or a nitrogen chain atom of

Y^3, thereby forming a ring which is optionally substituted with alkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, alkoxy, hydroxyl, hydroxylalkyl, carboxyl, halo, haloalkyl, amino, aminoalkyl, nitro, cyano, aryloxy, heteroaryloxy, aralkoxy, heteroaralkoxy, alkylcarbonyloxy, alkyloxycarbonyl, arylcarbonyloxyalkyl, aryloxycarbonylalkyl, alkylcarbonyl, formyl, oxo, aminocarbonyl, alkylcarbonylamino, alkylsulfonylamino, aminosulfonyl, aminocarbonyloxy, or alkyloxycarbonylamino. A is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, cycloalkenyl, heterocycloalkenyl, aryl, heteroaryl, aralkyl, heteroaralkyl, alkoxy, hydroxyl, hydroxylalkyl, thio, carboxyl, halo, haloalkyl, amino, aminoalkyl, alkylcarbonyloxy, alkyloxycarbonyl, alkylcarbonyl, alkylcarbonylamino, aminocarbonyl, alkylsulfonylamino, aminoisulfonyl, sulfonic acid, or alkylsulfonyl. Note that neither R^1 nor R^2 is a hydrogen and at least one of R^1 and R^2 contains a cyclic moiety having 3 to 20 ring atoms or a straight chain having 4 to 24 chain atoms.

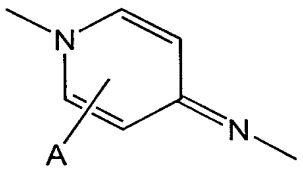
A further aspect of this invention relates to *N*-substituted pyridyl cyanoguanidine compounds of formula (II):



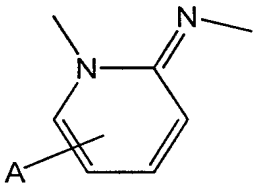
(II

R^1 is $-X^1-Y^1-X^2-R^a-X^3-Y^2-X^4-R^b$ and R^2 is $-X^5-Y^3-X^6-R^c-X^7-Y^4-X^8-R^d$. Each of X^1, X^2, X^3, X^4, X^5, X^6, X^7, and X^8, independently, is a bond, or a C_{1-6} alkylene chain optionally containing a double bond or a triple bond and further optionally substituted with alkyl, alkenyl, alkynyl, alkoxy, hydroxyl, halo, carboxyl, amino, nitro, cyano, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, aminosulfonyl, alkylsulfonylamino, alkylcarbonyloxy, alkyloxycarbonyl, alkylcarbonyl, formyl, alkylcarbonylamino, or aminocarbonyl. Each of Y^1, Y^2, Y^3, and Y^4, independently, is a bond, -O-, -S-, -SO-, $-SO_2-$, $-N(R^x)-$, -CO-, $-N(R^x)-CO-$, $-CO-N(R^x)-$, $-N(R^x)-SO_2-$, $-SO_2-N(R^x)-$, $-N(R^x)-CO-O-$, $-O-CO-N(R^x)-$, $-N(R^x)-CO-$

$N(R^y)$-, -O-CO-, -CO-O-, -O-SO_2-, or -SO_2-O- where each of R^x and R^y, independently, is hydrogen, alkyl, hydroxylalkyl, amino, cyano, haloalkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, aralkyl, or heteroaralkyl. Each of R^a and R^c, independently, is a bond, or cycloalkyl, heterocycloalkyl, cycloalkenyl, heterocycloalkenyl, aryl, or heteroaryl, optionally substituted with alkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, alkoxy, hydroxyl, hydroxylalkyl, carboxyl, halo, haloalkyl, amino, aminoalkyl, nitro, cyano, aryloxy, heteroaryloxy, aralkoxy, heteroaralkoxy, alkylcarbonyloxy, alkyloxycarbonyl, arylcarbonyloxyalkyl, aryloxycarbonylalkyl, alkylcarbonyl, formyl, aminocarbonyl, alkylcarbonylamino, alkylsulfonylamino, aminosulfonyl, aminocarbonyloxy, or alkyloxycarbonylamino. Each of R^b and R^d, independently, is hydrogen or a cyclic moiety having 3-20 ring atoms, optionally substituted with alkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, alkoxy, hydroxyl, hydroxylalkyl, carboxyl, halo, haloalkyl, amino, aminoalkyl, nitro, cyano, aryloxy, heteroaryloxy, aralkoxy, heteroaralkoxy, alkylcarbonyloxy, alkyloxycarbonyl, arylcarbonyloxyalkyl, aryloxycarbonylalkyl, alkylcarbonyl, formyl, oxo, aminocarbonyl, alkylcarbonylamino, alkylsulfonylamino, aminosulfonyl, aminocarbonyloxy, or alkyloxycarbonylamino. R^3 is



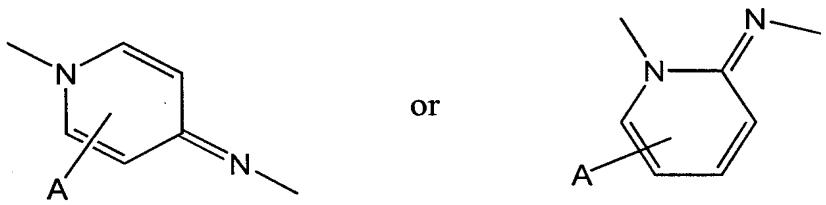
or



where the pyridine ring is bonded to R^1 and A is H, alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, cycloalkenyl, heterocycloalkenyl, aryl, heteroaryl, aralkyl, heteroaralkyl, alkoxy, hydroxyl, hydroxylalkyl, thio, carboxyl, halo, haloalkyl, amino, aminoalkyl, alkylcarbonyloxy, alkyloxycarbonyl, alkylcarbonyl, alkylcarbonylamino, aminocarbonyl, alkylsulfonylamino, aminoisulfonyl, sulfonic acid, or alkylsulfonyl. R^4 is hydrogen, alkyl, alkoxy, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, alkylcarbonyloxy, alkyloxycarbonyl, alkylcarbonyl, alkylcarbonylamino, or alkylaminocarbonyl.

Note that neither R^1 nor R^2 is a hydrogen and at least one of R^1 and R^2 contains a cyclic moiety having 3 to 20 ring atoms or a straight chain having 4 to 24 chain atoms.

A still further aspect of this invention relates to a *N*-substituted pyridyl cyanoguanidine compounds of formula (II), *supra*. R^1 is $-X^1-Y^1-X^2-R^a-X^3-Y^2-X^4-R^b$; and R^2 is $-X^5-Y^3-X^6-R^c-X^7-Y^4-X^8-R^d$; in which each of X^1, X^2, X^3, X^4, X^5, X^6, X^7, and X^8, independently, is a bond, or a C_{1-6} alkylene chain optionally containing a double bond or a triple bond and further optionally substituted with alkyl, alkenyl, alkynyl, alkoxy, hydroxyl, halo, carboxyl, amino, nitro, cyano, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, aminosulfonyl, alkylsulfonylamino, alkylcarbonyloxy, alkyloxycarbonyl, alkylcarbonyl, formyl, alkylcarbonylamino, or aminocarbonyl. Each of Y^1, Y^2, Y^3, and Y^4, independently, is a bond, -O-, -S-, -SO-, $-SO_2-$, $-N(R^x)-$, -CO-, $-N(R^x)-CO-$, $-CO-N(R^x)-$, $-N(R^x)-SO_2-$, $-SO_2-N(R^x)-$, $-N(R^x)-CO-O-$, $-O-CO-N(R^x)-$, $-N(R^x)-CO-N(R^y)-$, -O-CO-, -CO-O-, $-O-SO_2-$, or $-SO_2-O-$ where each of R^x and R^y, independently, is hydrogen, alkyl, hydroxylalkyl, amino, cyano, haloalkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, aralkyl, or heteroaralkyl. Each of R^a and R^c, independently, is a bond, or cycloalkyl, heterocycloalkyl, cycloalkenyl, heterocycloalkenyl, aryl, or heteroaryl, optionally substituted with alkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, alkoxy, hydroxyl, hydroxylalkyl, carboxyl, halo, haloalkyl, amino, aminoalkyl, nitro, cyano, aryloxy, heteroaryloxy, aralkoxy, heteroaralkoxy, alkylcarbonyloxy, alkyloxycarbonyl, arylcarbonyloxyalkyl, aryloxycarbonylalkyl, alkylcarbonyl, formyl, aminocarbonyl, alkylcarbonylamino, alkylsulfonylamino, aminosulfonyl, aminocarbonyloxy, or alkyloxycarbonylamino. Each of R^b and R^d, independently, is hydrogen or a cyclic moiety having 3-20 ring atoms, optionally substituted with alkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, alkoxy, hydroxyl, hydroxylalkyl, carboxyl, halo, haloalkyl, amino, aminoalkyl, nitro, cyano, aryloxy, heteroaryloxy, aralkoxy, heteroaralkoxy, alkylcarbonyloxy, alkyloxycarbonyl, arylcarbonyloxyalkyl, aryloxycarbonylalkyl, alkylcarbonyl, formyl, oxo, aminocarbonyl, alkylcarbonylamino, alkylsulfonylamino, aminosulfonyl, aminocarbonyloxy, or alkyloxycarbonylamino. R^3 is



where the pyridine ring is bonded to R^1 and A is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, cycloalkenyl, heterocycloalkenyl, aryl, heteroaryl, aralkyl, heteroaralkyl, alkoxy, hydroxyl, hydroxylalkyl, thio, carboxyl, halo, haloalkyl, amino, aminoalkyl, alkylcarbonyloxy, alkyloxycarbonyl, alkylcarbonyl, alkylcarbonylamino, aminocarbonyl, alkylsulfonylamino, aminoisulfonyl, sulfonic acid, or alkylsulfonyl. R^4 is a C_{1-4} alkylene chain in which the terminal carbon atom not bonded to the guanidinyl nitrogen atom is bonded to a carbon chain atom of X^5 or X^6, or a nitrogen chain atom of Y^3, thereby forming a ring which is optionally substituted with alkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, alkoxy, hydroxyl, hydroxylalkyl, carboxyl, halo, haloalkyl, amino, aminoalkyl, nitro, cyano, aryloxy, heteroaryloxy, aralkoxy, heteroaralkoxy, alkylcarbonyloxy, alkyloxycarbonyl, arylcarbonyloxyalkyl, aryloxycarbonylalkyl, alkylcarbonyl, formyl, oxo, aminocarbonyl, alkylcarbonylamino, alkylsulfonylamino, aminosulfonyl, aminocarbonyloxy, or alkyloxycarbonylamino. Note that neither R^1 nor R^2 is a hydrogen and at least one of R^1 and R^2 contains a cyclic moiety having 3 to 20 ring atoms or a straight chain having 4 to 24 chain atoms.

Set forth below are some examples of *N*-substituted pyridyl cyanoguanidine compounds of formula (I) and formula (II): 4-(*N*'-(6-(4-chloro-phenoxy)-hexyl)-*N*''-cyano-guanidino)-1-methyl-pyridinium, iodide; *N*-(6-(4-chloro-phenoxy)-hexyl)-*N*'-)1-(2-hydroxy-ethyl)-pyridin-4-yl)-*N*''-cyano-guanidine; 4-(*N*-(4-(5-dimethylamino-naphthalene-1-sulfonylamino)-benzyl)-*N*'-cyano-carbamimidoylmethyl)-1-methyl-pyridinium iodide; 5-dimethylamino-naphthalene-1-sulfonic acid (4-(*N*'-cyano-*N*''-(1-methyl-1*H*-pyridin-4-ylidene)-guanidinomethyl)-phenyl)-amide; *N*-(6-(4-chloro-phenoxy)-hexyl)-*N*'-cyano-*N*''-(1-methyl-1*H*-pyridin-4-ylidene)-guanidine; and *N*-(6-(4-chloro-phenoxy)-hexyl)-*N*'-(1-(2-hydroxy-ethyl)-1*H*-pyridin-4-ylidene)-*N*''-cyano-guanidine.

It should be recognized that the counterion of the positively charged *N*-substituted pyridyl cyanoguanidine compound of formula (I) is not shown in that formula itself. A counterion of a compound of formula (I) can either be an internal counterion or an external counterion. The term "internal counterion" refers to an anion which is a part of the compound, e.g., a carboxylate substituent. By contrast, "external counterion" refers to an anion that is associated with the compound via non-covalent bonding, e.g., electrostatic interaction. Some examples of such an external counterion are sulfate, pyrosulfate bisulfate, sulfite, bisulfite, phosphate, monohydrogenphosphate, dihydrogenphosphate, metaphosphate, pyrophosphate, chloride, bromide, iodide, acetate, propionate, decanoate, caprylate, acrylate, formate, isobutyrate, caprate, heptanoate, propiolate, oxalate, malonate, succinate, suberate, sebacate, fumarate, and maleate.

A salt of a compound of formula (II) is also within the scope of this invention. A salt of this compound can be formed between a negatively charged substituent (e.g., carboxylate) and a cationic counterion (e.g., sodium ion, potassium ion, magnesium ion, calcium ion, unsubstituted or substituted ammonium ion such as tetramethyl ammonium ion or diisopropylethyl ammonium ion); or between a positively charged substituent (e.g., amino) and an anionic counterion as listed above.

Note that two adjacent substituents on the pyridine ring can join together to form a 4- to 7-membered cyclic moiety together with the two atoms to which the substituents are bonded. For example, substituents bonded to the nitrogen ring atom and the 2-carbon atom of the pyridine ring, or substituents bonded to the 2- and the 3-carbon atoms of the pyridine ring can join together to form a cyclic moiety. The cyclic moiety can be cycloalkyl, heterocycloalkyl, cycloalkenyl, heterocycloalkenyl, aryl, or heteroaryl. Heteroatoms such as nitrogen, oxygen, and sulfur can be included in the cyclic moiety.

A compound of formula (I) or (II) of this invention may contain chiral carbon atoms. The optical isomers or diastereoisomers of a compound of this invention are all within the scope of this invention.

At least one of R^1 and R^2 of the compounds of formula (I) or formula (II) is required to contain a cyclic moiety having 3 to 20 ring atoms or a straight chain having 4 to 24 chain atoms. As used herein, a cyclic moiety is cycloalkyl,

heterocycloalkyl, cycloalkenyl, heterocycloalkenyl, aryl, or heteroaryl. A cyclic moiety can also be fused rings and can be formed from two or more of the just-mentioned groups. Examples of such a cyclic moiety include cyclopropyl, cyclohexyl, piperidinyl, morphilinyl, cyclooctenyl, pyranyl, phenyl, pyridinyl, benzofuryl, fluorenyl, dibenzocyclo-heptenyl, dihydro-dibenzoazepine, 7H-pyrazino[2,3-c]carbazole, or 9,10-dihydro-9,10-[2]butenoanthracene.

A straight chain refers to a hydrocarbon chain which may contain one or more (e.g., 1-12) double or triple bonds and may also contain heteroatoms such as nitrogen, oxygen, or sulfur in the chain itself. For example, R^1 can be 3-methyloctyl which has a straight chain containing 8 chain atoms.

Note that in some N-substituted pyridyl cyanoguanidine compounds of this invention, the terminal carbon atom of R^4 that is not bonded to the guanidinyl nitrogen atom can be bonded to a carbon chain atom of X^5 or X^6, or a nitrogen chain atom of Y^3. A chain atom is an atom on the main chain of a N-substituted pyridyl cyanoguanidine compound, i.e., the chain that connects R^1 and R^2. For example, if R^4 is a C_2 alkylene chain and X^5 is a C_3 alkylene chain, the teminal carbon atom of R^3 not bonded to the guanidinyl nitrogen atom can be bonded to the C_3 carbon atom of X^1, thereby forming a piperidine ring.

As used herein, alkyl is a straight or branched hydrocarbon chain containing 1 to 12 carbon atoms. Examples of alkyl include, but are not limited to, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, n-pentyl, 2-methylhexyl, 3-ethyloctyl, and 4-ethyldecyl.

The terms "alkenyl" and "alkynyl" refer to a straight or branched hydrocarbon chain containing 2 to 12 carbon atoms and containing one or more (e.g., 1-6) double or triple bonds, respectively. Some examples of alkenyl and alkynyl are allyl, 2-butenyl, 2-pentenyl, 2-hexenyl, 2-butynyl, 2-pentynyl and 2-hexynyl.

As used herein, a C_{1-6} alkylene chain is a divalent hydrocarbon chain containing 1-6 carbon atoms. For example, a C_1 alkylene chain and a C_2 alkylene chain refer to a methylene and an ethylene group, respectively.

By cycloalkyl is meant a cyclic alkyl group containing 3 to 8 carbon atoms. Some examples of cycloalkyl are cyclopropyl, cyclopentyl, cyclohexyl, cycloheptyl, adamantyl, and norbornyl. Heterocycloalkyl is a cycloalkyl group containing 1-3 heteroatoms such as nitrogen, oxygen, or sulfur. Examples of heterocycloalkyl include piperidinyl, piperazinyl, tetrahydropyranyl,

tetrahydrofuryl, and morpholinyl. Cycloalkenyl is a cycloalkyl group containing one or more (e.g., 1-3) double bonds. Examples of such a group include cyclopentenyl, 1,4-cyclohexa-di-enyl, cycloheptenyl, and cyclooctenyl groups. By the same token, heterocycloalkenyl is a heterocycloalkyl group containing one or more double bonds.

As used herein, aryl is an aromatic group containing 6-12 ring atoms and can contain fused rings, which may be saturated, unsaturated, or aromatic. Examples of an aryl group include phenyl, naphthyl, biphenyl, phenanthryl, and anthracyl. Heteroaryl is aryl containing 1-3 heteroatoms such as nitrogen, oxygen, or sulfur. Some examples of heteroaryl are pyridyl, furanyl, pyrrolyl, thienyl, thiazolyl, oxazolyl, imidazolyl, indolyl, benzofuranyl, and benzthiazolyl. Note that an amino group can be unsubstitued, mono-substituted, or di-substituted. It can be substituted with groups such as alkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, aralkyl, or heteroaralkyl. Halo refers to fluoro, chloro, bromo, or iodo and heteroatom refers to nitrogen, oxygen, or sulfur. N-substituted pyridyl cyanoguanidine compounds of this invention were found to possess an unexpectedly low toxicity. Other features or advantages of the present invention will be apparent from the following detailed description of several embodiments, and also from the appending claims.

DETAILED DESCRIPTION

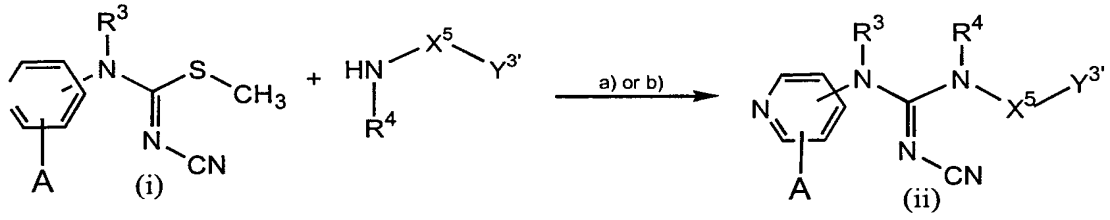
A compound of formulas (I) can be prepared from a pyridyl cyanoguanidine having a pyridine ring with an unsubstituted nitrogen ring atom (i.e., compound (iii) below). Compound (iii) can be prepared by a number of methods.

Referring to the schemes below, two methods (1) and (2) are described. Each of these methods employ a common starting material, S-methyl-*N*-cyano-*N'*-pyridylisothiourea or compound (i) below. For preparation of compound (i), see Schou et al., Bioorganic & Medicinal Chemistry Letters, 7(24), 3095-3100 (1997).

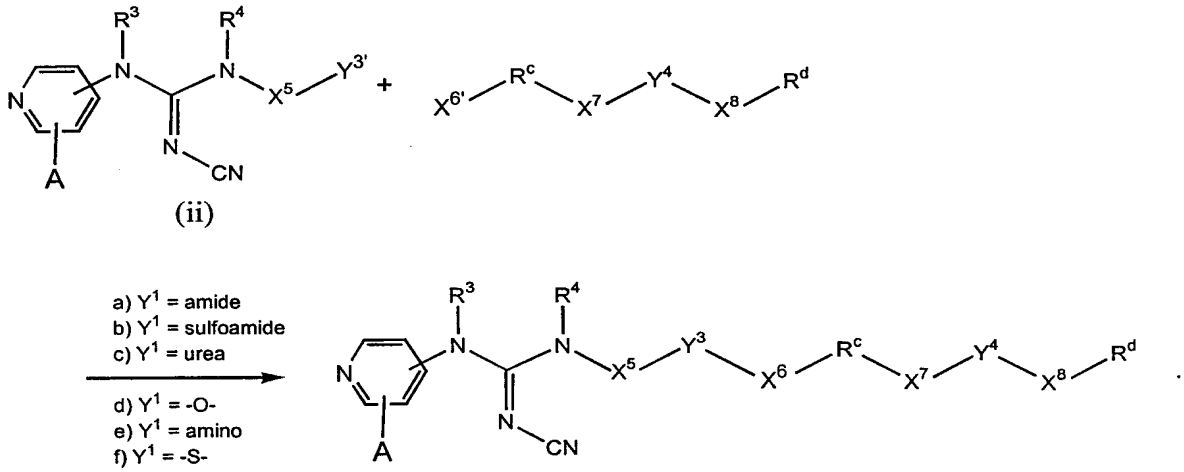
In the synthetic scheme of method (1), the definitions of R^3, R^4, R^c, R^d, X^5, X^6, X^7, X^8, Y^3, and Y^4 have been provided above. Compound (i) is first coupled with a primary amine or a secondary amine, $NH(R^4)$-X^5-$Y^{3'}$, to yield an

intermediate, compound (ii), which is then coupled with $X^{6'}$-R^c-X^7-Y^4-X^8-R^d to yield the desired pyridyl cyanoguanidine compound. Secondary amines include cyclic amines such as substituted piperidinyl or piperazinyl. Note that $Y^{3'}$ and $X^{6'}$ are functionalities which, upon reacting with each other, yield moieties of Y^3 and X^6, respectively. For example, if the desired Y^3 moiety is an amide, it can be formed by reacting an amine group ($Y^{3'}$) with a carboxyl group ($X^{6'}$) in the presence of a common coupling reagent such as benzotriazol-1-yloxytris(dimethylamino)-phosphonium hexafluorophosphate (BOP) or *O*-benzotriazol-1-yl-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (HBTU). The scheme below also includes conditions of the coupling reaction in which five other Y^3 moieties, i.e., sulfonamide, urea, oxygen, amino, and sulfur linkages, are formed.

Method (1)



a) Triethylamine, (4-dimethylamino)pyridine, pyridine, 60 °C (6-12 hours)
b) Triethylamine, (4-dimethylamino)pyridine, ethanol, 60 °C (4 hours)

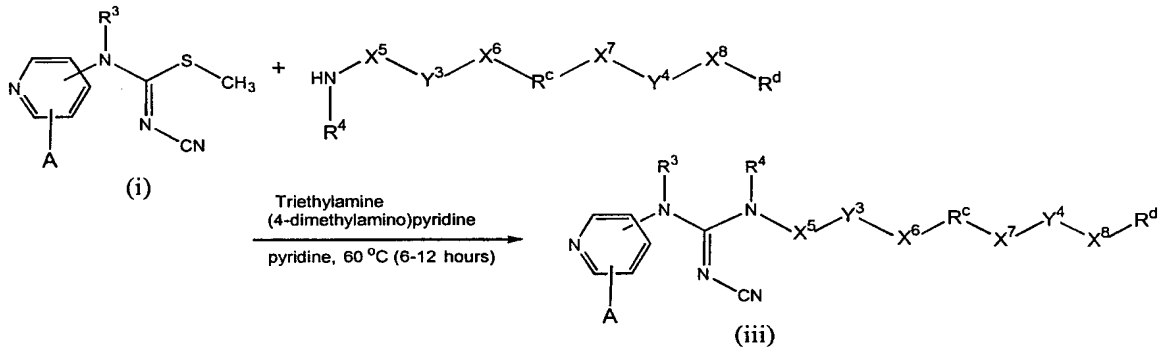


a) Diisopropylethylamine, benzotriazol-1-yloxy-tris(dimethylamino)phosphonium, dimethylformamide, room temperature
b) Pyridine, room temperature
c) Triethylamine, dimethylformamide, tetrahydrofuran, room temperature
d) Triphethylamine, diethylazodicarboxylate, tetrahydrofuran, room temperature
e) Sodium triacetoxyborohydride, glacial acetic acid, tetrahydrofuran, room temperature
f) Sodium hydroxide, Aliquat 336, tetrahydrofuran, room temperature

Alternatively, compound (i) can be first coupled with $NH(R^4)$-X^5-Y^3-X^6-R^c-X^7-$Y^{4'}$ to form an intermediate, which then reacts with $X^{8'}$-R^d to form a pyridyl cyanoguanidine compound of this invention. Similar to $Y^{3'}$ and $X^{6'}$, $Y^{4'}$ and $X^{8'}$ are functionalities, upon reacting with each other, yield moieties of Y^4 and X^8, respectively.

The scheme below shows an alternative method of preparing compound (iii). According to method (2), $NH(R^4)$-X^5-$Y^{3'}$ first reacts with $X^{6'}$-R^c-X^7-Y^4-X^8-R^d to form an intermediate $NH(R^4)$-X^5-Y^3-X^6-R^c-X^7-Y^4-X^8-R^d, which, in turn, is coupled with compound (i) to form compound (iii).

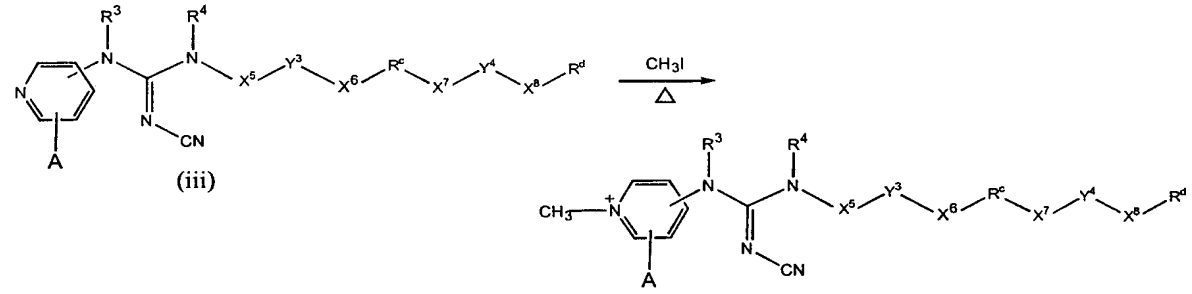
Method (2)



(i) (iii)

Compounds of formula (iii) in which R^c is a nitrogen-containing cyclic moiety, e.g., piperidinyl or imidazolyl, can be prepared by reacting $NH(R^4)$—X^5-Y^3-X^6-R^c with $X^{7'}$-Y^4-X^8-R^d to form an intermediate $NH(R^4)$-X^5-Y^3-X^6-R^c-X^7-Y^4-X^8-R^d before further reacting with compound (i). For example, $X^{7'}$ can contain a leaving group, e.g., -Cl, and undergo a substitution reaction with R^c, e.g., piperidine, to yield the desired intermediate, which can further react with compound (i) to form compound (iii) .

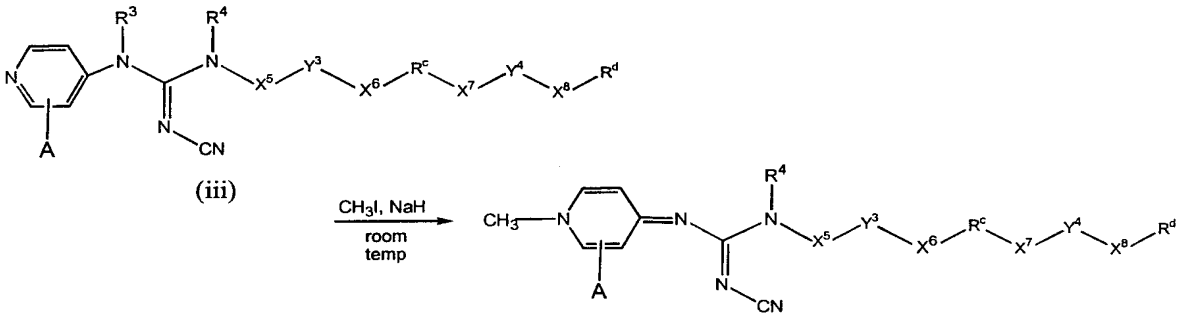
Compound (iii) then undergoes a substitution reaction with an electrophile to yield a compound of formula (I). An example is shown below in which compound (iii) is methylated by reacting with methyl iodide at an elevated temperature, e.g., 80-100°C.

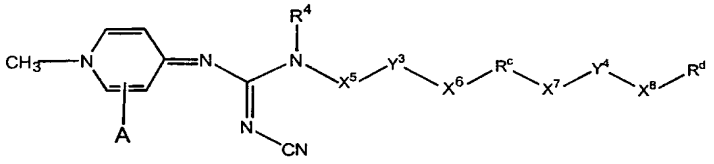


(iii)

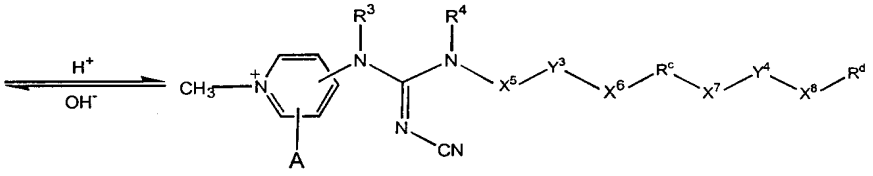
Compound (iii) can also undergo an amination reaction to form a compound of formula (I). See Org. Syn. Coll. Vol. V, 43 (1973) and Example 5 below.

A compound of formula (II) can also be prepared from compound (iii), *supra*. An additional base, e.g., sodium hydride, is needed to be present in the reaction. For example, if a methylated 4-pyridyl cyanoguanidine compound of formula (II) is desired, it can be prepared as depicted in the following reaction. Note that under acidic conditions, the compound of formula (II) can be reversibly converted to a compound of formula (I).





Formula (I)



Formula (II)

Note that appropriate protecting groups may be needed to avoid forming side products during the preparation of a pyridyl cyanoguanidine compound. For example, the amino group of $NH(R^4)$-X^5-$Y^{3'}$ can be first protected by a suitable amino protecting group such as trifluoroacetyl or *tert*-butoxycarbonyl prior to coupling with $X^{6'}$-R^c-X^7-Y^4-X^8-R^d. See, e.g., T. W. Greene, "Protective Groups

in Organic Synthesis," John Wiley & Sons, Inc., New York (1981), for more amino protecting groups.

An *N*-substituted pyridyl cyanoguanidine of formula (I) or (II) can be purified by methods such as crystallization.

The *N*-substituted pyridyl cyanoguanidines of both formula (I) and formula (II) can be used as antitumor agents. However, they display different pharmacokinetics properties. In general, a compound of formula (II), when administered orally, has a slower absorption rate into plasma as compared with the corresponding compound of formula (I). In other words, a compound of formula (II) has a longer blood clearance time than its counterpart of formula (I). It should be noted that a compound of formula (II) is converted to a compound of formula (I) under acidic conditions, e.g., in the stomach.

A pharmaceutical composition containing an effective amount of *N*-substituted pyridyl cyanoguanidine compound of formula (I) or formula (II) of this invention is also within the scope of this invention. Some examples of tumors which can be treated by this pharmaceutical composition are leukemia, lung cancer, colon cancer, CNS cancer, melanoma, ovarian cancer, cervical cancer, renal cancer, prostate cancer, and breast cancer. The use of such a compound of formula (I) or (II) for the manufacture of a medicament for treating the above-mentioned tumors is also within the scope of this invention. Still another aspect of this invention is a method of treating tumor by administering to a patient such a pharmaceutical composition containing an effective amount of a compound of formula (I), or a compound of formula (II) or its salt. An effective amount is defined as the amount which is required to confer a therapeutic effect on the treated patient, and is typically determined based on age, surface area, weight, and condition of the patient. The interrelationship of dosages for animals and humans (based on milligrams per meter squared of body surface) is described by Freireich et al., Cancer Chemother. Rep. 1966, 50, 219. Body surface area may be approximately determined from height and weight of the patient. See, e.g., Scientific Tables, Geigy Pharmaceuticals, Ardley, New York, 1970, 537. An effective amount of a compound of formula (I) or (II) can range from about 1 mg/kg to about 150 mg/kg. Effective doses will also vary, as recognized by those skilled in the art, dependant on route of administration, excipient usage, and the

possibility of co-usage with other therapeutic treatments including use of other antitumor agents and radiation therapy.

The pharmaceutical composition may be administered via the parenteral route, including orally, topically, subcutaneously, intraperitoneally, intramuscularly, and intravenously. Examples of parenteral dosage forms include aqueous solutions of the active agent, in a isotonic saline, 5% glucose or other well-known pharmaceutically acceptable excipient. Solubilizing agents such as cyclodextrins, or other solubilizing agents well-known to those familiar with the art, can be utilized as pharmaceutical excipients for delivery of the therapeutic compounds.

A compound of formula (I) or (II) of this invention can be formulated into dosage forms for other routes of administration utilizing conventional methods. For example, it can be formulated in a capsule, a gel seal, or a tablet for oral administration. Capsules may contain any standard pharmaceutically acceptable materials such as gelatin or cellulose. Tablets may be formulated in accordance with conventional procedures by compressing mixtures of a compound of formula (I) or (II) with a solid carrier and a lubricant. Examples of solid carriers include starch and sugar bentonite. The compound of formula (I) or (II) can also be administered in a form of a hard shell tablet or a capsule containing a binder, e.g., lactose or mannitol, a conventional filler, and a tableting agent.

The antitumor activity of a compound of formula (I) or (II) can be evaluated by MTS colorimetric assay (see Example 90 below). Results obtained by using cell lines of various types of tumors are compared with those obtained by using cell lines of normal cells in this assay. Viability of the cells in each cell line is estimated by measuring the cellular conversion of a tetrazolium salt after incubating the cells in a solution containing a test compound in a 96 well plate. IC_{50} values obtained by using an identical test compound on normal cells and cells of a particular tumor cell line are compared and their ratio ($IC_{50\ \text{normal cell}}/IC_{50\ \text{cancer cell}}$) indicates the cancer selectivity of that test compound. The higher the ratio, the higher the selectivity of the test compound towards that particular type of cancer cell.

The antitumor activity of a pyridyl cyanoguanidine compound of this invention can also be evaluated by *in vivo* testing, e.g., human tumor xenograft regression assays. Animals bearing established tumors are treated with a test

compound for a three-week period. The growth of the tumors and the general health of the animal are monitored during the three-week treatment and for two more weeks after treatment to determine if tumor regrowth occurs. See Example 91 below.

The toxicity of a compound of this invention can be evaluated by preliminary sub-acute toxicity study and acute toxicity study. See Examples 92 and 93 below.

The following specific examples, which describe syntheses and biological testings of compounds of formula (I) or (II) of this invention, are to be construed as merely illustrative, and not limitative of the remainder of the disclosure in any way whatsoever.

In the following examples, ^1H nuclear magnetic resonance spectra were recorded on a Varian Mercury 300 MHz spectrometer and ES mass spectra were recorded on a Finnigan Navigator mass spectrometer.

Without further elaboration, it is believed that one skilled in the art can, based on the description herein, utilize the present invention to its fullest extent. The following specific examples, which described syntheses, screenings, and biological testings of various compounds of this invention, are therefore, to be construed as merely illustrative, and not limitative of the remainder of the disclosure in any way whatsoever. All publications recited herein, including patents, are hereby incorporated by reference in their entirety.

Example 1

1-Methoxycarbonylmethyl-4-(*N*'-cyano-*N*''-(naphthalene-1-sulfonylamino)-benzyl)-guanidino)pyridium chloride (SBR-21-2808)

In this example, the desired product, which is a compound of formula (I), was prepared via an intermediate, naphthalene-1-sulfonic acid (4-(*N*'-cyano-*N*''-pyridin-4-yl-guanidinomethyl)-phenyl)-amide. This intermediate was prepared in accordance with method (1) as described above.

N-(4-Amino-benzyl)-*N*'-cyano-*N*''-quinolin-5-yl-guanidine (400 mg, 1.50 mmol) and 1-naphthalenesulfonyl chloride (340 mg, 1.50 mmol) were combined in pyridine (15 mL). An exothermic reaction occurred and the suspension became homogeneous. This solution was shaken at room temperature for 12 hours. The reaction mixture was then diluted with ethyl acetate (80 mL) and

washed with water (30 mL x 3). The organic phase was dried over anhydrous sodium sulfate. The solvent was removed in vacuo and the residue was purified by HPLC (yield = 150 mg).

A reaction vial was charged with naphthalene-1-sulfonic acid (4-(*N*'-cyano-*N*''-pyridin-4-yl-guanidinomethyl)-phenyl)-amide (40 mg, 0.087 mmol), 1,4-dioxane (1 ml), and methyl chloroacetate (77 µl, 0.87 mmol). The vial was placed under an atmoshpere of dry nitrogen, capped and heated with stirring in an oil bath at 100 °C for 4.5 hours. After cooling to room temperature, the reaction mixture was diluted with ether (5 ml) and allowed to stir for 20 minutes. The off-white solids which formed were collected by vacuum filtration, rinsed with ether (15 ml) and air-dried to give 47 mg of the desired product. ^{1}H NMR (DMSO-*d*6, ppm): 11.5 (bs, 1H), 10.85 (s, 1H), 9.1 (bs, 1H), 8.4 (d, 1H), 8.46 (bs, 2H), 8.2 (d, 2H), 8.05 (d, 2H), 7.55-7.8 (m, 3H), 7.45 (bs, 2H), 7.15 (d, 2H), 7.05 (d, 2H), 5.4 (s, 2H), 4.4 (s, 2H), 3.75 (s, 2H). MS (cald): 529.9; (measured): 529.9.

Example 2

1-(2-Bromo-allyl)-4-(*N*'-(6-(4-chloro-phenoxy)-hexyl)-*N*''-cyano-guanidino)-pyridinium; bromide (SBR-21-2802)

The title compound, which is of formula (I), was prepared via an intermediate, *N*-(6-(4-chloro-phenoxy)-hexyl)-*N*'-ethyl-*N*''-pyridin-4-yl-guanidine.

6-(4-Chloro-phenoxy)-hexylamine hydrobromide (3.40 g, 11 mmol) was dissolved in pyridine (8 mL). Triethylamine (2.8 mL, 20 mmol) was added followed by (4-dimethylamino)pyridine (5.0 mg, 0.04 mmol). The reaction mixture was stirred at 60° C for 18 hours. After cooling to room temperature, the reaction mixture was diluted with diethyl ether (100 mL). The resulting precipitate was collected by filtration and washed with diethyl ether. The crude product was recrystalized from methanol to give *N*-(6-(4-chloro-phenoxy)-hexyl)-*N*'-ethyl-*N*''-pyridin-4-yl-guanidine as a white crystalline solid in 88% yield.

In another reaction vial, *N*-(6-(4-chloro-phenoxy)-hexyl)-*N*'-ethyl-*N*''-pyridin-4-yl-guanidine (40 mg, 0.11 mmol), toluene (2 mL), and 2,3-dibromopropene (140 µL, 1.1 mmol) were added. The vial was placed under an atmosphere of dry nitrogen, capped and heated with

stirring in an oil bath at 100° C for 4.5 hours. After cooling to room temperature, the reaction mixture was diluted with ether (10 mL) and allowed to stir for 20 minutes. The off-white solids which formed were collected by vacuum filtration, rinsed with ether (25 mL) and air-dried to give 57 mg of the desired product. ^{1}H NMR (DMSO-d6, ppm): 8.9 (bs, 1H), 8.6 (d, 2H), 7.6 (bs, 2H), 7.30 (d, 2H), 6.95 (d, 2H), 6.26 (s, 1H), 5.95 (s, 1H), 5.4 (s, 2H), 3.95 (t, 2H), 1.3-1.8 (m, 8H). MS (cald): 492; (measured): 492.

Example 3

N-(6-(4-Chloro-phenoxy)-hexyl)-*N*'-cyano-*N*''-(1-methyl-1*H*-pyridin-4-ylidene)-guanidine (SBR-11-3552)

In this example, the title compound, which is of formula (II), was prepared directly via the corresponding pyridyl cyanoguanidine (with a non-alkylated pyridyl nitrogen atom).

In a dry reaction vial under a nitrogen atmosphere with magnetic stirring, *N*-(6-(4-chloro-phenoxy)-hexyl)-*N*'-ethyl-*N*''-pyridin-4-yl-guanidine (400 mg, 1.08 mmol) was dissolved in 4 mL of dry DMF and sodium hydride (60% in mineral oil, 48 mg, 1.3 mmol) was added. After stirring at room temperature for 2 hours, the reaction mixture was cooled to 0°C and methyl iodide (80 µl, 1.3 mmol) was added dropwise. The reaction mixture was then stirred at 0°C for 1.5 hours, and at room temperature for a further 2 hours. The reaction mixture was then diluted with 40 mL of water. The white solids which formed were collected by vacuum filtration and rinsed with water (80 mL). The solid was dried in vacuo to give the desired product (375 mg). ^{1}H NMR (DMSO-d6, ppm): 7.5-7.8 (2d, 2H), 7.32 (d, 2H), 6.96 (d, 2H), 6.7 (bs, 0.5H), 6.18 (s, 1.5H), 3.95 (bs, 2H), 3.6 (s, 3H), 3.1 (m, 2H), 1.2-1.8 (m, 8H).

Example 4

N-(1-(2-Bromo-allyl)-1*H*-pyridin-4-ylidene]-*N*'-(6-(4-chloro-phenoxy)-hexyl)-*N*''-cyano-guanidine (SBR-21-2842)

In this example, the title compound, which is of formula (II), was prepared via its corresponding compound of formula (I), i.e., SBR-21-2802, see Example 2 above.

In a round bottom flask with magnetic stirring 1-(2-

bromo-allyl)-4-(*N*'-(6-(4-chloro-phenoxy)-hexyl)-*N*''-cyano-guanidino)-pyridinium; bromide (20 mg, 0.03 mmol) is suspended in tetrahydrofuran (0.5 ml) and 2 M aqueous sodium hydroxide (0.04 mL, 0.08 mmol) solution is added. The solution becomes homogeneous and is allowed to stir at room temperature for 30 minutes. Ethyl acetate (5 mL) is added and the reaction mixture is washed with water (5 mL), dried over sodium sulfate and filtered through a plug of silica gel with ethyl acetate (20 mL). Concentration in vacuo gives 12.2 mg (74%) of the desired product. ^{1}H NMR (DMSO-*d*6, ppm) 7.65 (bs, 1H), 7.54 (d, 1H), 7.30 (d, 2H), 6.94 (d, 2H), 6.17 (d, 1H), 6.01 (bs 1H), 5.78 (bs, 1H), 4.81 (bs, 1H), 3.95 (bs, 2H), 3.10 (m, 2H), 1.70 (m, 2H), 1.4-1.2 (m, 8H). MS (cald): 489.11; (measured): 490.1.

Example 5

N-(6-(4-Chloro-phenoxy)-hexyl)-*N*'-cyano-*N*''-(1-amino-pyridin-4-yl)-guanidine (SBR-11-3724)

In a reaction flask with magnetic stirring *N*-[6-(4-Chloro-phenoxy)-hexyl]-*N*'-ethyl-*N*''-pyridin-4-yl-guanidine (115 mg, 0.3 mmol), hydroxylamine-O-sulfonic acid (36 mg, 0.3 mmol), and potassium carbonate (102 mg, 0.73 mmol) were combined in 3 ml of water. The mixture was heated to 85°C for 15 hours at which time a further 50 mg (0.4 mmol) of hydroxylamine-O-sulfonic acid was added and heating was continued for 2 more hours. The solvent was removed in vacuo and the resulting material was taken up in 10 ml of ethanol. The solids were removed by vacuum filtration and the filtrate was evaporated to give the pure product in 60% yield. ^{1}H NMR (DMSO-*d*6, ppm) 7.60-7.80 (d, 2H), 7.35 (d, 2H), 6.90 (d, 2H), 6.6 (d, 2H), 3.95 (bs, 2H), 3.2 (m, 2H), 1.4-1.8 (m, 8H).

In the table below, the columns "NMR," "Mass (Cald)," and "M" refer to ^{1}H nuclear magnetic resonance data, the calculated mass, and the measured mass of the named compound in each of Examples 6-89.

Examples 6-89

In the following examples, the identification codes, compound names, NMR and mass data, and the charged/neutral form (i.e., formula (I)/formula (II)) are shown in the table below. Note that some of the compounds have not been fully characterized.

Example	Compound ID	Name	NMR	Mass (Cald)	M	Formula
6	SBR-11-3551	4-(*N*-(6-(4-Chloro-phenoxy)-hexyl)-*N*"-cyano-guanidino)-1-methyl-pyridinium; iodide	(DMSO-d_6, ppm): 10.8 (bs, 1H), 8.9 (s, 1H), 8.56 (d, 2H), 7.54 (bs, 2H), 7.30 (d, 2H), 6.94 (d, 2H), 4.11 (s, 3H), 3.95 (t, 2H), 1.3-1.8 (m, 8H)	386.2	386.2	(I)
7	SBR-11-3701	(4-(*N*-)6-(4-Chloro-phenoxy)-hexyl)-*N*"-cyano-guanidino)-pyridin-1-yl)-acetic acid methyl ester	(DMSO-d_6, ppm): 8.9 (bs, 1H), 8.5 (d, 2H), 7.54 (bs, 2H), 7.32 (d, 2H), 6.96 (d, 2H), 5.4 (s, 2H), 3.9 (t, 2H), 3.8 (s, 3H), 1.2-1.8 (m,8H)	444.1	444.1	(I)
8	SBR-11-3702	*N*-(6-(4-Chloro-phenoxy)-hexyl)-*N*'-)1-(2-hydroxy-ethyl)-pyridin-4-yl)-*N*"-cyano-guanidine	(DMSO-d_6, ppm): 10.8(bs, 1H), 8.76(bs, 1H), 8.6(d, 2H), 7.56(bs, 2H), 7.51(d, 2H), 6.94(d, 2H), 5.2(bs, 1H), 4.42(t, 2H), 3.8(t, 2H), 1.3-1.8(m, 8H)	416	416	(I)
9	SBR-11-3760	4-(*N*-(6-(4-Chloro-phenoxy)-hexyl)-*N*"-cyano-guanidino)-1-cyanomethyl-pyridinium; chloride	(DMSO-d_6, ppm): 8.62 (bs, 2H), 7.5 (bs, 2H), 7.30 (d,2H), 6.93 (d, 2H), 5.65 (s, 2H), 3.35 (t, 2H,)1.2-1.8 (m, 8H)	411.1	411.1	(I)

10	SBR-11-3761	1-Benzyl-4-(*N*'-(6-(4-chloro-phenoxy)-hexyl)-*N*''-cyano-guanidino)-pyridinium	(DMSO-d_6, ppm): 8.85 (d, 2H), 7.55 (bs, 2H), 7.43 (s, 5H), 7.30 (d, 2H), 6.93 (d, 2H), 5.6 (s, 2H), 3.95 (t, 2H), 1.3-1.8 (m, 8H)	462.2	462.2	(I)
11	SBR-11-3777	(4-(*N*'-(6-(4-Chloro-phenoxy)-hexyl)-*N*''-cyano-carbamimidoylimino)-4*H*-pyridin-1-yl)-acetic acid methyl ester	(DMSO-d_6, ppm): 7.64 (s, 1H), 7.50 (d, 2H), 7.3 (d, 2H), 6.93 (d, 2H), 6.46 (bs, 0.5H), 6.67 (d, 1.5 H), 4.84 (s, 2H), 3.94 (t, 3H), 3.8 (s, 3H), 3.1(m,2H)1.2-1.8 (m, 8H)	441.1	441.1	(I)
12	SBR-11-3882	1-Methyl-4-(*N*'-cyano-*N*''-(4-(2,4,6-trimethyl-benzenesulfonylamino)-benzyl)-guanidino)-pyridinium; iodide	(DMSO-d_6, ppm): 10.87 (bs, 1H), 10.24 (s, 1H), 9.07 (bs, 1H), 8.57 (d, 2H), 7.53 (bs, 2H), 7.19 (d, 2H), 7.00 (s, 2H), 6.96 (d, 2H), 4.42 (d, 2H), 4.11 (s, 3H), 2.55 (s, 6H), 2.22 (s, 3H)	463.19	463.3	(I)
13	SBR-11-3883	1-Cyanomethyl-4-(*N*'-cyano-*N*''-(4-(2,4,6-trimethyl-benzenesulfonylamino)-benzyl)-guanidino)-pyridinium; chloride	(DMSO-d_6, ppm): 10.25 (s, 1H), 9.24 (bs, 1H), 8.66 (d, 2H), 7.53 (bs, 2H), 7.20 (d, 2H), 7.00 (s, 2H), 6.96 (d, 2H), 5.69 (s, 2H), 4.43 (d, 2H), 2.55 (s, 6H), 2.22 (s, 3H)	488.19	488.2	(I)

14	SBR-11-3884	1-Methoxycarbonylmethyl-4-(*N'*-cyano-*N''*-(4-(2,4,6-trimethyl-benzenesulfonylamino)-benzyl)-guanidino)-pyridinium; chloride	(DMSO-d_6, ppm): 10.24 (s, 1H), 9.26 (bs, 1H), 8.55 (bs, 2H), 7.59 (bs, 2H), 7.21 (d, 2H), 7.00 (s, 2H), 6.96 (d, 2H), 5.39 (s, 2H), 4.45 (d, 2H), 3.76 (s, 3H), 2.55 (s, 6H), 2.21 (s, 3H)	521.2	521.3	(I)
15	SBR-11-3885	1-Benzyl-4-(*N'*-cyano-*N''*-(4-(2,4,6-trimethyl-benzenesulfonylamino)-benzyl)-guanidino)-pyridinium; chloride	(DMSO-d_6, ppm): 11.36 (bs, 1H), 10.24 (s, 1H), 9.17 (bs, 1H), 8.75 (d, 2H), 7.60 (bs, 2H), 7.43 (s, 5H), 7.19 (d, 2H), 6.99 (s, 2H), 6.95 (d, 2H), 5.61 (s, 2H), 4.45 (d, 2H), 2.54 (s, 6H), 2.21 (s, 3H)	539.22	539.4	(I)
16	SBR-11-3886	1-(2-Hydroxy-ethyl)-4-(*N'*-cyano-*N''*-(4-(2,4,6-trimethyl-benzenesulfonylamino)-benzyl)-guanidino)-pyridinium; bromide	(DMSO-d_6, ppm): 10.24 (s, 1H), 9.12 (bs, 1H), 8.59 (d, 2H), 7.58 (bs, 2H), 7.19 (d, 2H), 7.00 (s, 2H), 6.96 (d, 2H), 5.20 (bs, 1H), 4.42 (m, 4H), 3.77 (t, 2H)	493.2	493.3	(I)
17	SBR-11-3889	1-(2-Hydroxy-ethyl)-4-(*N'*-cyano-*N''*-(4-(naphthalene-1-sulfonylamino)-benzyl)-guanidino)-pyridinium; bromide	(DMSO-d_6, ppm): 10.9 (s, 1H), 9.05 (s, 1H), 9.00 (s, 1H), 8.75 (d, 1H), 8.58 (d, 2H), 8.23 (d, 2H), 8.08 (d, 1H), 7.4-7.8 (m, 5H), 7.14 (d, 2H), 7.03 (d, 2H), 5.2 (s, 1H), 3.7 (bs, 2H), 4.35 (m, 4H)	501.4	501.4	(I)

18	SBR-11-3894	4-)*N*-Cyano-*N*"-(6-phenyl-hexyl)-guanidino)-1-methyl-pyridinium; iodide	(DMSO-d_6, ppm): 10.78 (bs, 1H), 8.68 (bs, 1H), 8.54 (d, 2H), 7.50 (bs, 2H), 7.17-7.30 (m, 5H), 4.09 (s, 3H), 3.32 (m, 2H), 2.57 (t, 2H), 1.55 (m, 4H), 1.32 (m, 2H)	336.22	336.2	(I)
19	SBR-11-3895	4-(*N*-(5-(4-Chloro-benzyloxy)-pentyl)-*N*"-cyano-guanidino)-1-methyl-pyridinium; iodide	(DMSO-d_6, ppm): 10.78 (bs, 1H), 8.70 (bs, 1H), 8.55 (d, 2H), 7.52 (bs, 2H), 7.32-7.42 (m, 5H), 4.44 (s, 2H), 4.10 (s, 3H), 3.43 (m, 4H), 1.57 (m, 4H), 1.37 (m, 2H)	386.17	386.2	(I)
20	SBR-11-3896	4-(*N*-Cyano-*N*"-)4-(3-trifluoromethyl-benzenesulfonylamino)-benzyl)-guanidino)-1-methyl-pyridinium; iodide	(DMSO-d_6, ppm): 10.75 (s, 1H), 9.0 (s, 1H), 8.73 (d, 1H), 8.55 (d, 2H), 8.22 (d, 2H), 8.07 (d, 1H), 7.6-7.8 (m, 3H), 7.5 (bs, 2H), 7.06 (d, 2H), 7.03 (d, 2H), 4.38 (d, 2H), 4.01 (s, 3H)	471.1	471.1	(I)
21	SBR-11-3913	1-(2-Hydroxy-ethyl)-4-(*N*-cyano-*N*"-(4-(3-trifluoromethyl-benzenesulfonylamino)-benzyl)-guanidino)-pyridinium; bromide	(DMSO-d_6, ppm): 10.97 (bs, 1H), 10.52 (s, 1H), 9.16 (bs, 1H), 8.62 (d, 2H), 8.03 (m, 3H), 7.81 (t, 1H), 7.57 (bs, 2H), 7.25 (d, 2H), 7.09 (d, 2H), 4.46 (m, 4H), 3.77 (t, 2H)	519.14	519.1	(I)

22	SBR-11-3914	1Cyanomethyl-4-(*N*-cyano-*N*"-(4-(3-trifluoromethyl-benzenesulfonylamino)-benzyl)-guanidino)-pyridinium; chloride	(DMSO-*d*6, ppm): 10.61 (s, 1H), 9.20 (bs, 1H), 8.78 (d, 2H), 8.12 (m, 3H), 7.90 (t, 1H), 7.68 (bs, 2H), 7.36 (d, 2H), 7.20 (d, 2H), 5.81 (s, 2H), 4.59 (s, 2H)	514.13	514.1	(I)
23	SBR-11-3915	1-Methyl-4-(*N*-cyano-*N*"-(4-(3-trifluoromethyl-benzenesulfonylamino)-benzyl)-guanidino)-pyridinium; iodide	(DMSO-*d*6, ppm): 10.92 (bs, 1H), 10.52 (s, 1H), 9.11 (bs, 1H), 8.59 (d, 2H), 8.03 (m, 3H), 7.82 (t, 1H), 7.57 (bs, 2H), 7.26 (d, 2H), 7.10 (d, 2H), 4.46 (d, 2H), 4.12 (s, 3H)	489.13	489.1	(I)
24	SBR-11-3945	3-(*N*-Cyano-*N*"-(4-(2,4,6-trimethyl-benzenesulfonylamino)-benzyl)-guanidino)-1-methyl-pyridinium; iodide	(DMSO-*d*6, ppm): 10.22 (s, 1H), 9.49 (bs, 1H), 9.01 (s, 1H), 8.68 (d, 2H), 8.34 (m, 2H), 8.04 (m, 1H), 7.18 (d, 2H), 7.00 (s, 2H), 6.96 (d, 2H), 4.40 (d, 2H), 4.31 (s, 3H)	463.19	463.2	(I)
25	SBR-11-3946	3-(*N*-Cyano-*N*"-(4-(naphthalene-1-sulfonylamino)-benzyl)-guanidino)-1-methyl-pyridinium; iodide	(DMSO-*d*6, ppm): 10.72 (s, 1H), 9.83 (bs, 1H), 8.97 (s, 1H), 8.72 (d, 1H), 8.66 (d, 1H), 8.29 (m, 2H), 8.21 (d, 2H), 8.06 (m, 2H), 7.60-7.74 (m, 3H), 7.11 (d, 2H), 7.01 (d, 2H), 4.34 (d, 2H), 4.29 (s, 3H)	471.16	471.2	(I)

26	SBR-11-3947	3-(*N*'-Cyano-*N*''-(4-(3-trifluoromethyl-benzenesulfonylamino)-benzyl)-guanidino)-1-methyl-pyridinium; iodide	(DMSO-*d*6, ppm): 10.60 (s, 1H), 10.00 (bs, 1H), 9.12 (s, 1H), 8.79 (d, 1H), 8.50 (m, 1H), 8.44 (d, 2H), 8.15 (m, 4H), 7.93 (t, 1H), 7.34 (d, 2H), 7.20 (d, 2H), 4.53 (d, 2H), 4.42 (s, 3H)	489.13	489.1	(I)
27	SBR-11-3948	4-(*N*'-Cyano-*N*''-(4-((9*H*-fluorene-9-carbonyl)-amino)-benzyl)-guanidino)-1-methyl-pyridinium	(DMSO-*d*6, ppm): 10.92 (bs, 1H), 10.73 (s, 1H), 9.18 (bs, 1H), 8.57 (d, 2H), 7.91 (d, 2H), 7.57-7.63 (m, 6H), 7.31-7.45 (m, 6H), 5.05 (s, 1H), 4.51 (d, 2H), 4.10 (s, 3H)	473.21	473.2	(I)
28	SBR-11-3949	3-(*N*-(6-(4-Chloro-phenoxy)-hexyl)-*N*'-cyano-carbamimidoyl)-1-methyl-pyridinium; iodide	(DMSO-*d*6, ppm): 9.61 (t, 1H), 9.41 (s, 1H), 9.16 (d, 1H), 8.85 (d, 1H), 8.34 (t, 1H), 7.31 (d, 2H), 6.95 (d, 2H), 4.42 (s, 3H), 3.97 (t, 2H), 3.44 (q, 2H), 1.73 (m, 2H), 1.64 (m, 2H), 1.44 (m, 4H)	371.16	371.2	(I)
29	SBR-11-3950	4-(*N*'-Cyano-*N*''-(4-(2-(6-methoxy-naphthalen-2-yl)-propionylamino)-benzyl)-guanidino)-1-methyl-pyridinium; iodide	(DMSO-*d*6, ppm): 10.85 (bs, 1H), 10.13 (s, 1H), 9.13 (bs, 1H), 8.56 (d, 2H), 7.77 (m, 4H), 7.58 (d, 2H), 7.55 (d, 2H), 7.26 (d, 3H), 7.15 (d, 1H), 4.47 (d, 2H), 4.09 (s, 3H), 3.95 (q, 1H), 3.86 (s, 3H), 1.48 (d, 3H)	493.24	493.2	(I)

30	SBR-11-3951	4-(*N'*-Cyano-*N''*-octadecyl-guanidino)-1-methyl-pyridinium; iodide	(DMSO-d_6, ppm): 10.77 (bs, 1H), 8.68 (bs, 1H), 8.55 (d, 2H), 7.53 (bs, 2H), 4.10 (s, 3H), 3.33 (q, 2H), 1.54 (m, 2H), 1.24 (m, 30H), 0.85 (t, 3H)	428.38	428.5	(I)
31	SBR-11-3962	1-Cyanomethyl-4-(*N'*-cyano-*N''*-(6-phenyl-hexyl)-guanidino)-pyridinium	(DMSO-d_6, ppm): 11.33 (bs, 1H), 8.92 (bs, 1H), 8.65 (d, 2H), 7.52 (bs, 2H), 7.16-7.29 (m, 5H), 5.69 (s, 2H), 3.35 (q, 2H), 2.59 (t, 2H), 1.55 (m, 2H), 1.33 (m, 2H)	361.21	361.2	(I)
32	SBR-11-3963	1-Methoxycarbonylmethyl-4-(*N'*-cyano-*N''*-(6-phenyl-hexyl)-guanidino)-pyridinium; chloride	(DMSO-d_6, ppm): 11.47 (bs, 1H), 8.93 (bs, 1H), 8.57 (d, 2H), 7.60 (bs, 2H), 7.17-7.27 (m, 5H), 5.41 (s,2H), 3.76 (s, 3H), 3.37 (q, 2H), 2.57 (t, 2H), 1.56 (m, 4H), 1.33 (m, 4H)	394.22	394.3	(I)
33	SBR-11-3964	1-Benzyl-4-(*N'*-cyano-*N''*-(6-phenyl-hexyl)-guanidino)-pyridinium	(DMSO-d_6, ppm): 11.27 (bs, 1H), 8.79 (bs, 1H), 8.76 (d, 2H), 7.61 (bs, 2H), 7.44 (m, 5H), 7.16-7.26 (m, 5H), 5.61 (s, 2H), 3.33 (q, 2H), 2.56 (t, 2H), 1.54 (m, 4H), 1.32 (m, 4H)	412.25	412.3	(I)

34	SBR-11-3965	4-(N'-Cyano-N''-(6-phenyl-hexyl)-guanidino)-1-(3-phenoxy-propyl)-pyridinium; bromide	(DMSO-d6, ppm): 10.88 (bs, 1H), 8.74 (bs, 1H), 8.71 (d, 2H), 7.58 (bs, 2H), 7.17-7.28 (m, 7H), 6.84 - 6.94 (m, 3H), 4.57 (t, 2H), 4.06 (t, 2H), 3.33 (q, 2H), 2.56 (t, 2H), 2.32 (t, 2H), 1.57 (m, 4H), 1.33 (m, 4H)	456.28	456.3	(I)
35	SBR-11-3966	4-(N'-Cyano-N''-(6-phenyl-hexyl)-guanidino)-1-(2-methyl-allyl)-pyridinium; bromide	(DMSO-d6, ppm): 11.02 (bs, 1H), 8.77 (bs, 1H), 8.59 (d, 2H), 7.58 (bs, 2H), 7.17-7.27 (m, 5H), 5.08 (s, 1H), 4.99 (s, 2H), 4.78 (s, 1H), 3.32 (q, 2H), 2.57 (t, 2H), 1.69 (s, 3H), 1.57 (m, 4H), 1.34 (m, 4H)	376.25	376.3	(I)
36	SBR-11-3967	4-(N'-Cyano-N''-(6-phenyl-hexyl)-guanidino)-1-pent-4-enyl-pyridinium; bromide	(DMSO-d6, ppm): 10.96 (bs, 1H), 8.73 (bs, 1H), 8.67 (d, 2H), 7.58 (bs, 2H), 7.17-7.29 (m, 5H), 5.80 (m, 1H), 5.02 (m, 2H), 4.37 (t, 2H), 3.33 (q, 2H), 2.56 (t, 2H), 2.03 (m, 2H), 1.93 (m, 2H), 1.55 (m, 2H), 1.33 (m, 4H)	390.27	390.3	(I)
37	SBR-11-3968	4-(N'-(5-(4-Chloro-benzyloxy)-pentyl)-N''-cyano-guanidino)-1-cyanomethyl-pyridinium; chloride	(DMSO-d6, ppm): 11.62 (bs, 1H), 8.96 (bs, 1H), 8.68 (d, 2H), 7.58 (bs, 2H), 7.41 (d, 2H), 7.34 (d, 2H), 5.71 (s, 2H), 4.44 (s, 2H), 3.40 (m, 4H), 1.58 (m, 4H), 1.38 (m, 2H)	411.17	411.2	(I)

38	SBR-11-3969	4-(*N*-(5-(4-Chloro-benzyloxy)-pentyl)-*N*''-cyano-guanidino)-1-methoxycarbonylmethyl-pyridinium; chloride	(DMSO-*d*6, ppm): 11.54 (bs, 1H), 8.95 (bs, 1H), 8.58 (d, 2H, 7.59 (bs, 2H), 7.40 (d, 2H), 7.34 (d, 2H), 5.42 (s, 2H), 4.44 (s, 2H), 3.76 (s, 3H), 3.43 (m, 4H), 1.58 (m, 4H), 1.38 (m, 4H)	444.18	444.2	(I)
39	SBR-11-3970	1-Benzyl-4-(*N*-(5-(4-chloro-benzyloxy)-pentyl)-*N*''-cyano-guanidino)-pyridinium	(DMSO-*d*6, ppm): 11.32 (bs, 1H), 8.88 (bs, 1H), 8.77 (d, 2H), 7.62 (bs, 2H), 7.31-7.46 (m, 9H), 5.62 (s, 2H), 4.43 (s, 2H), 3.42 (m, 4H), 1.56 (m, 4H), 1.37 (m, 2H)	462.21	462.2	(I)
40	SBR-11-3971	4-(*N*-(5-(4-Chloro-benzyloxy)-pentyl)-*N*''-cyano-guanidino)-1-(3-phenoxy-propyl)-pyridinium; bromide	(DMSO-*d*6, ppm): 10.95 (bs, 1H), 8.78 (bs, 1H), 8.71 (d, 2H), 7.59 (bs, 2H), 7.25-7.41 (m, 6H), 6.84-6.95 (m, 3H), 4.57 (t, 2H), 4.44 (s, 2H), 4.04 (t, 2H), 3.43 (t, 2H), 3.41 (m, 2H), 2.31 (m, 2H), 1.57 (m, 4H), 1.38 (m, 2H)	506.23	506.3	(I)
41	SBR-11-3972	4-(*N*-(5-(4-Chloro-benzyloxy)-pentyl)-*N*''-cyano-guanidino)-1-(2-methyl-allyl)-pyridinium; bromide	(DMSO-*d*6, ppm): 11.05 (bs, 1H), 8.80 (bs, 1H), 8.59 (d, 2H), 7.60 (bs, 2H), 7.40 (d, 2H), 7.33 (d, 2H), 5.08 (s, 1H), 4.99 (s, 2H), 4.78 (s, 1H), 4.44 (s, 2H), 3.41 (m, 4H), 1.69 (s, 3H), 1.57 (m, 4H), 1.38 (m, 2H)	426.21	426.2	(I)

42	SBR-11-3973	4-(*N*-(5-(4-Chloro-benzyloxy)-pentyl)-*N*''-cyano-guanidino)-1-pent-4-enyl-pyridinium; bromide	(DMSO-d_6, ppm): 10.95 (bs, 1H), 8.75 (bs, 1H), 8.68 (d, 2H), 7.59 (bs, 2H), 7.40 (d, 2H), 7.34 (d, 2H), 5.80 (m, 1H), 5.04 (m, 2H), 4.44 (s, 2H), 4.37 (t, 2H), 3.43 (t, 2H), 3.36 (m, 2H), 2.03 (, 2H), 1.96 (m, 2H), 1.58 (m, 4H), 1.38 (m, 2H)	440.22	440.2	(I)
43	SBR-11-3985	4-(*N*-(6-(4-Cyano-3-methoxy-phenoxy)-hexyl)-*N*''-cyano-guanidino)-1-methyl-pyridinium; iodide	(DMSO-d_6, ppm): 10.80 (bs, 1H), 8.73 (bs, 1H), 8.57 (d, 2H), 7.57 (bs, 2H), 7.39 (d, 2H), 7.11 (d, 1H), 4.11 (s, 3H), 4.06 (t, 2H), 3.81 (s, 3H), 3.37 (q, 2H), 1.74 (m, 2H), 1.59 (m, 2H), 1.41 (m, 4H)	407.22	407.3	(I)
44	SBR-11-3986	4-(*N*-(6-(4-Chloro-3-nitro-phenoxy)-hexyl)-*N*''-cyano-guanidino)-1-methyl-pyridinium; iodide	(DMSO-d_6, ppm): 10.80 (bs, 1H), 8.73 (bs, 1H), 8.57 (d, 2H), 7.64 (d, 2H), 7.57 (bs, 2H), 7.29 (d, 1H), 4.12 (s, 3H), 4.06 (t, 2H), 3.37 (q, 2H), 1.74 (m, 2H), 1.58 (m, 2H), 1.41 (m, 4H)	431.16	431.2	(I)
45	SBR-11-3999	4-(*N*-Cyano-*N*''-(4-(naphthalene-1-sulfonylamino)-benzyl)-guanidino)-1-(2-methyl-allyl)-pyridinium; bromide	(DMSO-d_6, ppm): 10.75 (s, 1H), 9.08 (s, 1H), 8.74 (d, 2H), 8.56 (d, 2H), 8.23 (d, 2H), 8.05 (d, 1H), 7.4-7.8 (m, 5H), 7.15 (d, 2H), 7.04 (d,2H), 5.1 (s, 1H), 4.75 (s, 1H), 4.36 (d, 2H), 1.68 (s, 3H)	511.3	511.3	(I)

46	SBR-11-4015	4-(*N*-Cyano-*N*''-(4-phenyl-butyl)-guanidino)-1-methyl-pyridinium; iodide	(DMSO-*d*6, ppm): 10.74 (bs, 1H), 8.70 (bs, 1H), 8.54 (s, 2H), 7.52 (bs, 2H), 7.19-7.28 (m, 5H), 4.10 (s, 3H), 3.38 (m, 2H), 2.60 (t, 2H), 1.60 (m, 4H)	308.19	308.2	(I)
47	SBR-11-4016	4-(*N*-Cyano-*N*''-(8-vinyl-dec-8-enyl)-guanidino)-1-methyl-pyridinium; iodide	(DMSO-*d*6, ppm): 10.80 (bs, 1H), 8.64 (bs, 1H), 8.55 (d, 2H), 7.56 (bs, 2H), 7.17-7.27 (m, 5H), 4.10 (s, 3H), 3.33 (m, 2H), 2.57 (t, 2H), 1.55 (m, 4H), 1.30 (m, 6H)	350.23	350.2	(I)
48	SBR-11-4017	4-(*N*-(2-(3,4-Bis-benzyloxy-phenyl)-ethyl)-*N*''-cyano-guanidino)-1-methyl-pyridinium; iodide	(DMSO-*d*6, ppm): 10.78 (bs, 1H), 8.72 (bs, 1H), 8.53 (d, 2H), 7.31-7.46 (m, 12H), 7.00 (m, 2H), 6.78 (d, 1H, 5.10 (s, 2H), 5.07 (s, 2H), 4.07 (s, 3H), 3.57 (q, 2H), 2.79 (t, 2H)	492.24	492.3	(I)
49	SBR-11-4018	4-(*N*-(6-(2,4-Difluoro-phenoxy)-hexyl)-*N*''-cyano-guanidino)-1-methyl-pyridinium; iodide	(DMSO-*d*6, ppm): 10.72 (bs, 1H), 8.72 (bs, 1H), 8.57 (d, 2H), 7.55 (bs, 2H), 7.17-7.27 (m, 2H), 6.99 (m, 1H), 4.11 (s, 3H), 4.01 (t, 2H), 3.40 (m, 2H), 1.72 (m, 2H), 1.58 (m, 2H), 1.41 (m, 4H)	388.19	388.3	(I)

50	SBR-11-4019	4-(*N*-Cyano-*N*''-(6-(4-methoxy-2-methyl-phenoxy)-hexyl)-guanidino)-1-methyl-pyridinium; iodide	(DMSO-*d*6, ppm): 10.80 (bs, 1H), 8.72 (bs, 1H), 8.57 (d, 2H), 7.56 (bs, 2H), 7.43 (s, 1H), 7.30 (d, 1H), 7.25 (d, 1H), 4.11 (s, 3H), 4.09 (t, 2H), 3.77 (s, 3H), 3.40 (m, 2H), 1.70 (m, 2H), 1.58 (m, 2H), 1.38 (m, 4H)	427.21	427.3	(I)
51	SBR-11-4020	4-(*N*-(5-(3,7-Dimethyl-oct-6-enylcarbamoyl)-pentyl)-*N*''-cyano-guanidino)-1-methyl-pyridinium; iodide	(DMSO-*d*6, ppm): 10.75 (bs, 1H), 8.69 (bs, 1H), 8.55 (d, 2H), 7.52 (bs, 2H), 5.06 (bs, 1H), 4.10 (s, 3H), 3.24 (bs, 2H), 3.03 (bs, 2H), 2.03 (m, 2H), 1.93 (m, 2H), 1.64 (s, 3H), 1.56 (s, 3H), 1.0-1.5 (m, 11H), 0.85 (d, 3H)	427.32	427.4	(I)
52	SBR-11-4021	1-Cyanomethyl-4-(*N*-cycloheptyl-*N*''-cyano-guanidino)-pyridinium chloride	(DMSO-*d*6, ppm): 11.65 (bs, 1H), 8.93 (bs, 1H), 8.60 (d, 2H), 7.44 (bs, 2H), 5.67 (s, 2H), 3.95 (m, 1H), 1.91 (m, 2H), 1.52 (m, 10H)	297.18	297.2	(I)
53	SBR-11-4022	4-(*N*-Cycloheptyl-*N*''-cyano-guanidino)-1-pent-4-enyl-pyridinium; bromide	(DMSO-*d*6, ppm): 10.98 (bs, 1H), 8.62 (bs, 1H), 8.51 (bs, 2H), 7.28 (bs, 2H), 5.82 (m, 1H), 5.02 (m, 2H), 4.28 (m, 2H), 3.87 (m, 1H), 2.02 (m, 2H), 1.92 (m, 4H), 1.55 (m, 10H)	326.23	326.2	(I)

54	SBR-11-4023	1-(2-Biphenyl-4-yl-2-oxo-ethyl)-4-(*N'*-cycloheptyl-*N''*-cyano-guanidino)-pyridinium; bromide	(DMSO-*d*6, ppm): 11.12 (bs, 1H), 8.84 (bs, 1H), 8.48 (m, 2H), 8.12 (d, 2H), 7.97 (d, 2H), 7.81 (d, 2H), 7.52 (m, 5H), 6.21 (s, 2H), 3.96 (m, 1H), 1.96 (m, 2H), 1.54 (m, 10H)	452.25	452.4	(I)
55	SBR-11-4024	4-(*N'*-Cyano-*N''*-(4-)(9*H*-fluorene-9-carbonyl)-amino)-benzyl)-guanidino)-1-(2-methyl-allyl)-pyridinium bromide	(DMSO-*d*6, ppm): 11.08 (bs, 1H), 10.74 (s, 1H), 9.21 (bs, 1H), 8.56 (d, 2H), 7.90 (d, 2H), 7.61 (m, 6H), 7.44 (m, 2H), 7.34 (m, 4H), 5.08 (s, 1H), 5.05 (s, 1H), 4.96 (s, 2H), 4.77 (s, 1H), 4.51 (d, 2H), 1.68 (s, 3H)	513.26	513.4	(I)
56	SBR-11-4025	4-(*N'*Cyano-*N''*-(4-((9*H*-fluorene-9-carbonyl)-amino)-benzyl)-guanidino)-1-methoxycarbonylmethyl-pyridinium; chloride	(DMSO-*d*6, ppm): 10.82 (s, 1H), 9.34 (bs, 1H), 8.54 (d, 2H), 7.91 (d, 2H), 7.58-7.92 (m, 6H), 7.32-7.46 (m, 6H), 5.39 (s, 2H), 5.07 (s, 1H), 4.54 (d, 2H), 3.76 (s, 3H)	531.21	531.4	(I)
57	SBR-11-4026	1-(l)llyloxycarbonylmethyl-4-(*N'*-(4-((9*H*-fluorene-9-carbonyl)-amino)-benzyl)-*N''*-cyano-guanidino)-pyridinium; chloride	(DMSO-*d*6, ppm): 10.82 (s, 1H), 9.32 (bs, 1H), 8.56 (d, 2H), 7.91 (d, 2H), 7.58-7.67 (m, 6H), 7.31-7.46 (m, 6H), 5.93 (m, 1H), 5.43 (s, 2H), 5.32 (m, 2H), 5.07 (s, 1H), 4.70 (d, 2H), 4.54 (d, 2H)	557.23	557.2	(I)

58	SBR-11-4027	4-(N-Cyano-N'-(4-((9H-fluorene-9-carbonyl)-amino)-benzyl)-guanidino)-1-(4-methoxycarbonyl-butyl)-pyridinium; bromide	(DMSO-d6, ppm): 10.75 (s, 1H), 9.20 (bs, 1H), 8.67 (d, 2H), 7.91 (d, 2H), 7.58-7.92 (m, 6H), 7.31-7.46 (m, 6H), 5.05 (s, 1H), 4.51 (d, 2H), 4.37 (t, 2H), 3.58 (s, 3H), 2.36 (t, 2H), 1.83 (m, 2H), 1.49 (m, 2H)	573.26	573.4	(I)
59	SBR-11-4028	4-(N-Cyano-N''-(4-)(9H-fluorene-9-carbonyl)-amino)-benzyl)-guanidino)-1-(4-methoxy-benzyl)-pyridinium; chloride	(DMSO-d6, ppm): 10.72 (s, 1H), 9.18 (bs, 1H), 8.64 (bs, 2H), 7.91 (d, 2H), 7.55-7.65 (m, 6H), 7.30-7.45 (m, 8H), 6.98 (d, 2H), 5.45 (s, 2H), 5.05 (s, 1H), 4.47 (d, 2H), 3.75 (s, 3H)	579.25	579.2	(I)
60	SBR-11-4029	4-(N-(4-((9H-Fluorene-9-carbonyl)-amino)-benzyl)-N''-cyano-guanidino)-1-(3-phenoxy-propyl)-pyridinium; bromide	(DMSO-d6, ppm): 10.75 (s, 1H), 9.20 (bs, 1H), 8.68 (d, 2H), 7.90 (d, 2H), 7.24-7.67 (m, 14H), 6.82-6.97 (m, 3H), 5.05 (s, 1H), 4.53 (m, 4H), 4.03 (t, 2H), 2.31 (m, 2H)	593.27	593.3	(I)
61	SBR-11-4030	1-(2-Biphenyl-4-yl-2-oxo-ethyl)-4-(N'-(4-((9H-fluorene-9-carbonyl)-amino)-benzyl)-N''-methyl-guanidino)-pyridinium; bromide	(DMSO-d6, ppm): 11.12 (bs, 1H), 10.75 (s, 1H), 9.32 (bs, 1H), 8.49 (bs, 2H), 8.12 (d, 2H), 7.97 (d, 2H), 7.91 (d, 2H), 7.81 (d, 2H), 7.32-7.68 (m, 15H), 6.21 (s, 2H), 5.05 (s, 1H), 4.53 (d, 2H)	653.27	653.2	(I)

62	SBR-11-4057	1-(6-Ethoxycarbonyl-hexyl)-4-(*N*-cyano-*N*"-(4-(naphthalene-1-sulfonylamino)-benzyl)-guanidino)-pyridinium; bromide	(DMSO-*d*6, ppm): 10.75 (s, 1H), 9.08 (s, 1H), 8.74 (d, 2H), 8.56 (d, 2H), 8.23 (d, 2H), 8.05 (d, 1H), 7.4-7.8 (m, 5H), 7.15 (d, 2H), 7.04 (d,2H), 4.36 (m, 4H), 4.05 (q, 2H), 2.15 (t, 2H), 1.5 (t, 2H), 1.26 (s, 4H), 1.17 (t, 3H)	613.3	613.3	(I)
63	SBR-11-4058	1-Hexyl-4-(*N*-cyano-*N*"-(4-(naphthalene-1-sulfonylamino)-benzyl)-guanidino)-pyridinium; bromide	(DMSO-*d*6, ppm): 10.75 (s, 1H), 9.08 (s, 1H), 8.74 (d, 2H), 8.56 (d, 2H), 8.23 (d, 2H), 8.05 (d, 1H), 7.4-7.8 (m, 5H), 7.15 (d, 2H), 7.04 (d,2H), 4.35 (m, 4H), 1.8 (bs, 2H), 0.85 (t, 3H)	541.3	541.3	(I)
64	SBR-11-4059	1-Hept-6-enyl-4-(*N*-cyano-*N*"-(4-(naphthalene-1-sulfonylamino)-benzyl)-guanidino)-pyridinium; bromide	(DMSO-*d*6, ppm): 10.75 (s, 1H), 9.08 (s, 1H), 8.74 (d, 2H), 8.56 (d, 2H), 8.23 (d, 2H), 8.05 (d, 1H), 7.4-7.8 (m, 5H), 7.15 (d, 2H), 7.04 (d,2H), 5.8 (m, 1H), 5.0 (m, 2H), 4.34 (m, 4H), 2.0 (m, 2H), 1.8 (m, 2H), 1.3 (bs, 8H)	567.6	567.6	(I)
65	SBR-11-4060	4-(*N*-Cyano-*N*"-(3-(naphthalene-1-sulfonylamino)-benzyl)-guanidino)-1-(3-phenoxy-propyl)-pyridinium; bromide	(DMSO-*d*6, ppm): 10.75 (s, 1H), 9.08 (s, 1H), 8.74 (d, 2H), 8.56 (d, 2H), 8.23 (d, 2H), 8.05 (d, 1H), 7.4-7.8 (m, 5H), 7.28 (dd, 2H), 7.15 (d, 2H), 7.04 (d,2H), 6.94 (t, 1H), 6.85 (d, 2H), 4.55 (t, 2H), 4. (d, 2H), 4.03 (t, 2H), 2.3 (m, 2H)	591.3	591.3	(I)

66	SBR-11-4061	4-(*N*-Cyano-*N*'-(4-(naphthalene-1-sulfonylamino)-benzyl)-guanidino)-1-(4-methoxycarbonyl-butyl)-pyridinium; bromide	(DMSO-*d*6, ppm): 10.75 (s, 1H), 9.08 (s, 1H), 8.74 (d, 2H), 8.56 (d, 2H), 8.23 (d, 2H), 8.05 (d, 1H), 7.4-7.8 (m, 5H), 7.15 (d, 2H), 7.04 (d,2H), 4.36 (m, 4H), 3.6 (s, 3H), 2.3 (t, 2H), 1.8 2(m, 2H), 1. 5(m, 2H)	571.3	571.3	(I)
67	SBR-11-4062	4-(*N*-Cyano-*N*'-(4-(naphthalene-1-sulfonylamino)-benzyl)-guanidino)-1-(3-phenyl-propyl)-pyridinium; bromide	(DMSO-*d*6, ppm): 10.75 (s, 1H), 9.08 (s, 1H), 8.74 (d, 2H), 8.56 (d, 2H), 8.23 (d, 2H), 8.05 (d, 1H), 7.4-7.8 (m, 5H), 7.0-7.4 (m, 9H), 4.4 (m, 4H), 2.6 (t, 3H), 2.17 (m, 2H)	575.22	575.22	(I)
68	SBR-11-4063	4-(*N*-Cyano-*N*'-(4-(naphthalene-1-sulfonylamino)-benzyl)-guanidino)-1-(4-methoxy-benzyl)-pyridinium; bromide	(DMSO-*d*6, ppm): 10.75 (s, 1H), 9.08 (s, 1H), 8.74 (d, 2H), 8.5 6(d, 2H), 8.23 (d, 2H), 8.05 (d, 1H), 7.4-7.8 (m, 7H), 6.9-7.4 (m, 5H), 5.5 (s, 2H), 4.38 (m, 2H), 3.76 (s, 3H)	577.3	577.3	(I)
69	SBR-11-3725	1-Amino 4-(*N*-(6-(4-chloro-phenoxy)-hexyl)-*N*"-methyl-guanidino)-pyridinium; iodide	(DMSO-*d*6, ppm): 10.3 (bs, 1H), 8.53 (m, 3H), 7.75 (m,1H), 7.5 (m, 2H), 7.3 (m, 2H), 6.95 (m, 2H), 3.36 (m, 2H), 1.7 (m, 2H), 1.58 (m, 2H), 1.4 (m, 4H)	387.89	387.2	(I)

70	SBR-11-4065	*N*-)6-(4-Chloro-phenoxy)-hexyl)-*N'*-(1-(2-hydroxy-ethyl)-1*H*-pyridin-4-ylidene)-*N''*-cyano-guanidine	(DMSO-*d*6, ppm): 8.0 (d, 0.25H), 7.3 (b, 3.75H), 6.9 (d, 2H), 6.8 (d, 0.25H), 6.0 (d, 1.175H), 3.6-3.9 (m, 5H), 2.8-3.2 (m, 3H), 1.3-1.7 (m, 8H)	417	417.1	(II)
71	SBR-21-2842	*N*-(1-(2-Bromo-allyl)-1*H*-pyridin-4-ylidene)-*N'*-(6-(4-chloro-phenoxy)-hexyl)-*N''*-cyano-guanidine	(DMSO-*d*6, ppm) 7.65 (bs, 1H), 7.54 (d, 1H), 7.30 (d, 2H), 6.17 (d, 1H), 6.01 (bs 1H), 5.78 (bs, 1H), 4.81 (bs, 1H), 3.95 (bs, 2H), 3.10 (m, 2H), 1.70 (m, 2H), 1.4-1.2 (m, 8H)	489.11	490.1 (M+1)	(II)
72	SBR-11-4067	*N*-(1-Benzyl-1*H*-pyridin-4-ylidene)-*N'*-)6-(4-chloro-phenoxy)-hexyl)-*N''*-methyl-guanidine	(DMSO-*d*6, ppm) 7.6 (bs, 2H), 7.3 (m, 7H), 6.9 (d, 2H), 6.4 (bs, 0.25H), 6.1 (bs, 1.75H), 5.1 (bs, 2H), 3.9 (t, 2H), 1.3-1.7 (m, 8H)	461.2	461.2	(II)
73	SBR-11-4068	*N*-(4-(*N'*-(1-(2-Hydroxy-ethyl)-1*H*-pyridin-4-ylidene)-*N''*-cyano-guanidinomethyl)-phenyl)-2,4,6-trimethyl-benzenesulfonamide	(DMSO-*d*6, ppm): 6.80 (d, 2H), 6.75 (s, 2H), 6.55 (d, 2H), 4.10 (d, 2H), 3.63 (bs, 1H), 3.47 (bs, 4H), 2.58 (s, 6H), 2.15 (s, 3H)			(II)

74	SBR-11-4069	Naphthalene-1-sulfonic acid (4-(*N*'-cyano-*N*''-(1-methyl-1*H*-pyridin-4-ylidene)-guanidinomethyl)-phenyl)-amide	(DMSO-*d*6, ppm) 9.1(d, 2H), 8.0 (d, 2H), 7.9 (d, 2H), 7.5 (m, 4H), 6.6 (m, 4H), 6.0 (bs, 2H), 4.1 (bs, 2H)	470.1	470.1	(II)
75	SBR-11-4070	9*H*-Fluorene-9-carboxylic acid (4-(*N*'-cyano-*N*''-(1-methyl-1*H*-pyridin-4-ylidene)-guanidinomethyl)-phenyl)-amide	(DMSO-*d*6, ppm) 8.0 (d, 2H), 7.9 (d, 2H), 7.7(d, 2H), 7.6 (b, 2H), 6.9-7.3 (m, 7H), 6.8 (t, 2H), 6.1 (bs, 2H), 4.2 (m, 3H)	472.2	472.2	(II)
76	SBR-11-4071	*N*-Cyano-*N*'-(1-pent-4-enyl-1*H*-pyridin-4-ylidene)-*N*''-(6-phenyl-hexyl)-guanidine	(DMSO-*d*6, ppm) 7.1-7.5 (m, 7H), 6.1-6.2 (bs, 2H), 5.8 (m, 1H), 5.1 (m, 2H), 3.8 (bs, 2H), 3.0 (bs, 2H), 2.6 (bs, 2H), 2.0 (d, 2H), 1.8 (t, 2H), 1.2-1.6 (m, 8H)	389.2	389.3	(II)
77	SBR-11-4072	*N*-Cyano-*N*'-(1-(3-phenoxy-propyl)-1*H*-pyridin-4-ylidene)-*N*''-(6-phenyl-hexyl)-guanidine	(DMSO-*d*6, ppm) 7.1- 7.6 (m, 9H), 6.9 (d, 3H), 6.0-6.4 (bm, 2H), 4.0 (bs, 4H), 3.0 (bs, 2H), 2.5 (bs, 2H), 2.1 (d, 2H), 1.2-1.6 (m, 8H)	455.3	455.4	(II)

78	SBR-11-4073	Naphthalene-1-sulfonic acid (4-(N'-cyano-N''-(1-(2-methyl-allyl)-1H-pyridin-4-ylidene)-guanidinomethyl)-phenyl)-amide	(DMSO-$d6$, ppm) 9.0 (d, 1H), 8.0 (d, 1H), 7.8 (d, 2H), 7.2-7.6 (m, 6H), 6.7 (m, 4H), 6.0-6.2 (bm, 2H), 4.9 (b, 1H), 4.7 (b, 1H), 4.3 (bs, 2H), 4.0 (bs, 2H)1.64 (s, 3H)	510.2	510.2	(II)
79	SBR-21-2801	2-Chloro-5-(N'-(6-(4-chloro-phenoxy)-hexyl)-N''-cyano-guanidino)-1-methyl-pyridinium; iodide	(DMSO-$d6$, ppm): 9.3 (s, 1H), 8.56 (d, 1H), 8.0 (m, 1H), 7.30 (d, 2H), 4.4 (s, 3H), 3.9 (t, 2H), 1.2-1.8 (m, 8H)	420.1	420.1	(I)
80	SBR-21-2809	1-Cyanomethyl-4-(N'-cyano-N''-(4-(naphthalene-1-sulfonylamino)-benzyl)-guanidino)-pyridinium; chloride	(DMSO-$d6$, ppm): 10.9 (s, 1H), 9.05 (s, 1H), 9.05 (s, 1H), 9.00 (s, 1H), 8.75 (d, 1H), 8.58 (d, 2H), 8.23 (d, 2H), 8.08 (d, 1H), 7.4-7.8 (m, 5H), 7.14 (d, 2H), 7.03 (d, 2H), 5.2 (s, 1H), 4.35 (m, 4H), 3.7 (bs, 2H)	496	496	(I)
81	SBR-21-2816	4-(N'-(4-(3-Benzyl-2-methyl-penta-2,4-dienoylamino)-benzyl)-N''-cyano-guanidino)-1-methyl-pyridinium; iodide	(DMSO-$d6$, ppm): 10.88 (bs, 1H), 10.40 (s, 1H), 9.21 (bs, 2H), 8.59 (d, 2H), 7.70 (d, 2H), 7.58 (bs, 2H), 7.19-7.47 (m, 11H), 4.53 (d, 2H), 4.12 (m, 5H)	475.22	475.2	(I)

82	SBR-21-2817	4-(*N*-Cyano-*N*''-(6-(2-methyl-3-nitro-phenoxy)-hexyl)-guanidino)-1-methyl-pyridinium; iodide	(DMSO-d_6, ppm): 10.75 (bs, 1H), 8.73 (bs, 1H), 8.57 (d, 2H), 7.55 (bs, 2H), 7.38 (d, 1H), 7.25 (t, 1H), 7.05 (d, 1H), 4.10 (s, 3H), 4.00 (t, 2H), 3.39 (m, 2H), 2.30 (s, 3H), 1.72 (m, 2H), 1.59 (m, 2H), 1.40 (m, 4H)	411.21	411.2	(I)
83	SBR-21-2818	1-(6-(4-Chloro-phenoxy)-hexyl)-4-(*N*'-cyano-*N*''-methyl-guanidino)-pyridinium; bromide	(DMSO-d_6, ppm): 10.97 (bs, 1H), 8.70 (bs, 1H), 8.69 (d, 2H), 7.69 (bs, 2H), 7.32 (d, 2H), 6.93 (d, 2H), 4.38 (t, 2H), 3.94 (t, 2H), 2.92 (d, 3H), 1.85 (m, 2H), 1.70 (m, 2H), 1.43 (m, 2H), 1.30 (m, 2H)	386.17	386.2	(I)
84	SBR-21-2819	1-(6-(4-Chloro-phenoxy)-hexyl)-4-(*N*'-cyano-*N*''-propyl-guanidino)-pyridinium; bromide	(DMSO-d_6, ppm): 11.03 (bs, 1H), 8.88 (bs, 1H), 8.68 (d, 2H), 7.60 (bs, 2H), 7.31 (d, 1H), 6.93 (d, 2H), 4.37 (t, 2H), 3.94 (t, 2H), 3.32 (q, 2H), 1.85 (m, 2H), 1.69 (m, 2H), 1.57 (m, 2H), 1.44 (m, 2H), 1.30 (m, 2H), 0.90 (t, 3H)	414.21	414.2	(I)
85	SBR-21-2820	4-(*N*-Benzyl-*N*''-cyano-guanidino)-1-(6-(4-chloro-phenoxy)-hexyl)-pyridinium; bromide	(DMSO-d_6, ppm): 10.97 (bs, 1H), 9.20 (bs, 1H), 8.65 (d, 2H), 7.55 (bs, 2H), 7.38 (m, 5H), 7.31 (d, 2H), 6.93 (d, 2H), 4.56 (d, 2H), 4.36 (t, 2H), 3.94 (t, 2H), 1.84 (m, 2H), 1.69 (m, 2H), 1.43 (m, 2H), 1.29 (m, 2H)	462.21	462.2	(I)

86	SBR-11-4085	5-Dimethylamino-naphthalene-1-sulfonic acid (4-(*N*'-cyano-*N*"-(1-methyl-1*H*-pyridin-4-ylidene)-guanidinomethyl)-phenyl)-amide	(DMSO-*d*6, ppm): 8.42 (m, 2H), 8.12 (d, 2H), 7.54 (m, 4H), 7.36 (bs, 1H), 7.21 (d, 1H), 7.01 (d, 2H), 6.98 (d, 2H), 6.32 (bs, 2H), 4.16 (d, 2H), 3.63 (s, 3H), 2.81 (s, 6H)	513.19	514.3 (M+1)	(II)
87	SBR-11-4086	4-(*N*'-(4-((9*H*-Fluorene-9-carbonyl)-amino)-benzyl)-*N*"-cyano-guanidino)-1-oct-7-enyl-pyridinium; bromide	(DMSO-*d*6, ppm): 10.98 (bs, 1H), 10.74 (s, 1H), 9.18 (bs, 1H), 8.66 (d, 2H), 7.91 (d, 2H), 7.31-7.66 (m, 12H), 5.78 (m, 1H), 5.05 (s, 1H), 5.03 (d, 1H), 4.95 (d, 1H), 4.51 (d, 2H), 4.34 (t, 2H), 2.00 (m, 2H), 1.81 (m, 2H), 1.30 (m, 6H)	569.3	569.5	(I)
88	SBR-11-4087	1-Biphenyl-4-ylmethyl-4-(*N*'-(4-((9*H*-fluorene-9-carbonyl)-amino)-benzyl)-*N*"-methyl-guanidino)-pyridinium; chloride	(DMSO-*d*6, ppm): 11.32 (bs, 1H), 10.81 (s, 1H), 9.22 (bs, 1H), 8.78 (d, 2H), 7.91 (d, 2H), 7.73 (d, 2H), 7.30-7.68 (m, 19H), 5.63 (s, 2H), 5.07 (s, 1H), 4.52 (d, 2H)	625.27	625.2	(I)
89	SBR-11-4088	4-(*N*'-(4-((9*H*-Fluorene-9-carbonyl)-amino)-benzyl)-*N*"-methyl-guanidino)-1-(3-phenyl-propyl)-pyridinium; bromide	(DMSO-*d*6, ppm): 10.98 (bs, 1H), 10.74 (s, 1H), 9.19 (bs, 1H), 8.66 (d, 2H), 7.91 (d, 2H), 7.65 (d, 2H), 7.58 (d, 2H), 7.18-7.46 (m, 13H), 5.05 (s, 1H), 4.53 (d, 2H), 4.40 (t, 2H), 2.60 (m, 2H), 2.15 (m, 2H)	577.27	577.3	(I)

Example 90

In vitro efficacy studies

In the primary screening, the test compounds were applied to a panel of five human cell lines at a concentration of 12.5 µM. From the results obtained in this primary screening, cytotoxic compounds were selected for testing against a panel of 27 cell lines at a range of different concentrations in the secondary

screening. The concentration of a test compound that produces a cytotoxicity level of 50% (IC_{50}) was determined.

Clonogenic assay was used in the primary screening. Cells were seeded at a low cell density in 96 well flat-bottom plates and incubated for 24 hours at 37□C in a 7% CO_2 atmosphere. The 5 cell lines used were: CX-1 (colon carcinoma), MDA-MB-435 (breast carcinoma), PC-3 (prostate carcinoma), H2 (leukemia), and CCD-39sk (normal skin fibroblasts).

N-substituted pyridyl cyanoguanidine compounds at 12.5 μM were then added in duplicate to the cell plates and incubated for 6 days under the same conditions. MTS colorimetric assay (Promega), which measures cell viability based on the cellular conversion of a tetrazolium salt, was performed directly in the 96 well plates at the end of the 6-day period. After the plates were read and recorded, viable adherent cells were stained with Crystal violet (Sigma) to verify the results obtained from the MTS assay.

IC_{50} values were determined in the secondary screening. Cells were seeded at a low cell density in 96 well flat-bottom plates and incubated for 24 hours at 37°C in a 7% CO_2 atmosphere. Cell lines used in this screening were: CX-1 (colon carcinoma), MIP-101 (colon carcinoma), HCT-116 (colon carcinoma), HCT-29 (colon carcinoma), HCT-15 (colon carcinoma), MDA-MB-435 (breast carcinoma), MCF-7 (breast carcinoma), PC-3 (prostate carcinoma), DU-145 (prostate carcinoma), H2 (leukemia), K562 (leukemia), HL-60 (leukemia), RL (non-Hodgkin's B cell lymphoma), A549 (lung carcinoma), H510A (small cell lung carcinoma), ME-180 (cervical carcinoma), HeLa (cervical carcinoma), 2008 (cervical carcinoma), C13 (cervical carcinoma, CDDP resistant), ES-2 (ovarian carcinoma), MIA PaCa2 (pancreatic carcinoma), ACHN (renal adenocarcinoma), HepG2 (liver carcinoma), LOX (melanoma), G3361 (melanoma), CCD-39sk (normal skin fibroblasts), and CV-1 (transformed monkey kidney cells).

N-substituted pyridyl cyanoguanidine compounds were added in duplicate in serial dilution from 0.005 to 10.0 μM to the cell plates. The cell plates were then incubated for 6 days under the same conditions. MTS assay was performed followed by staining of viable adherent cells with Crystal violet after the 6-day period. The results obtained from Crystal violet stained plates were used to compare and verify those obtained from the MTS assay.

For PC-3 prostate tumor cells, among the thirty six compounds tested, twenty one of them were shown to have IC_{50} values less than 1 μM; eleven were shown to have IC_{50} values less than 0.05 μM and three were shown to have IC_{50} values as low as less than 0.005 μM. For MDA-MB-435 mammary carcinoma cells, among the thirty six compounds tested, seventeen of them had IC_{50} values less than 1 μM, ten had IC_{50} values less than or equal to 0.05 μM and two had IC_{50} values less than 0.005 μM. For CX-1 colon carcinoma cells, among the thirty six compounds tested, nine of them had IC_{50} values of less than 1 μM and six had IC_{50} values less than 0.05 μM. For ME-180 cervical carcinoma cells, among the forty three compounds testsed, eleven of them had IC_{50} values of less than 1 μM, four compounds had IC_{50} values less than 0.05 μM and three had IC_{50} values less than 0.005 μM. For RL lymphoma cells, among the forty three compounds testsed, fifteen of them were shown to have IC_{50} values of less than 1 μM, eight were shown to have IC_{50} values less than 0.05 μM and four were shown to have IC_{50} values less than 0.005 μM. Some compounds including SBR-11-3701, SBR-11-3702, SBR-11-3886, SBR-21-2802, and SBR-21-2809 were cytotoxic against several cells lines at IC_{50} values of less than 1 μM.

More importantly, there are several compounds that were shown to be specifically targeting tumor cells in comparison to normal cells. For example, when comparing the IC_{50} values for normal skin fibroblasts (CCD-39sk) to a tumor cell line (PC-3), sixteen out of thirty six compounds tested showed a greater than 50-fold selectivity and six demonstrated a 1000-fold or greater cytotoxic selectivity toward tumor cells compared to normal cells.

Example 91

In vivo efficacy studies

From the in vitro results obtained, *N*-substituted pyridyl cyanoguanidine compounds are selected for human tumor xenograft regression assays. Animals bearing established tumors (RL) are treated with a test compound for a three-week period. The growth of the tumors and the general health of the animals are monitored during the treatment and for an additional two weeks after dosing is terminated to determine if tumor regrowth takes place.

Non-Hodgkin's B cell lymphoma (RL) tumor cells, which are adapted to grow as solid tumors, are implanted by an intradermal injection of a tumor cell suspension

(30×10^6 cells in 0.1 mL media) in the flanks of female NIH Swiss nude mice (Taconic Labs). Each mouse is implanted with one tumor and 6-8 mice per group are used.

Dosing is initiated one week after implantation (Day 1), when tumors reached approximately 50 to 100 mm^3 in volume, with a test compound or vehicle five times per week for three weeks either intravenously (IV) or intraperitoneally (IP). Cyclophosphamide (CTX, Sigma) is used as a standard in the assays. Compounds are first dissolved in DMSO (Sigma) and formulated with 20% Cremophor RH40 (BASF) to a final concentration of 10% DMSO / 18% Cremophor. The formulated solution is made fresh daily.
Tumors, assumed to be hemi-ellipsoid in shape, are measured with calipers in three dimensions. Tumor volumes are calculated using the equation:

$$\text{Volume} = 1/2\ (L/2 \times W/2 \times H)\ 4/3\ \pi$$

where L = length, W = width, and H = height of the tumor. Animals are weighed and their general health is monitored during the course of the assay. When tumors become necrotic or if animals become moribund, the animals are euthanized by CO_2 asphyxiation. Student's t test is used to determine if there is a significant difference between the data obtained in the compound treated group and the vehicle treated group.

Example 92

Acute toxicity studies

Female SW mice with body weights over 20g were used in the acute toxicity study. The mice were divided into three groups: untreated, treated with vehicle, and treated with a pyridyl cyanoguanidine test compound. Three mice were assigned to each group and were given doses by a single intravenous bolus administration. The highest doses tested produced acute lethal or significantly toxic effects. The experiment lasted for one week. The mortality, clinical signs of toxicity, and body weight of each animal were monitored and recorded every day or every other day. Necropsy and gross examinations of major organs were performed on the animals which died during the study as well as those sacrificed at the end of the experiment. Histopathogical evaluations were conducted on 2-3 Hematoxylin and Eosin stained tissue sections from major organs including the heart, liver, kidneys, lungs and spleen, of the animals which died or were treated with the highest doses of test compounds. Compounds SBR-11-3551 and SBR-11-3552 were tested and found to possess unexpectedly low toxicity. Their toxic doses (LD_{50}) were determined to be 150 mg/kg and 200 mg/kg, respectively.

Example 93

Preliminary sub-acute toxicity studies

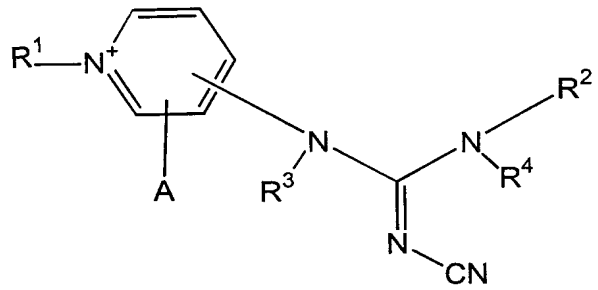
The preliminary sub-acute toxicity study is carried out in parallel on the same animals used in the efficacy study. After continuous treatment for 3 weeks with repeated intravenous and intraperitoneal dosing, three out of eight animals are sacrificed in each treatment group. The remaining animals are sacrificed two weeks later. Necropsy, liver weight, gross examinations of visible abnormalities in the major organs, and limited histological studies are conducted in all animals. In addition, blood chemistry tests and complete blood cell count analyses are performed in most of the animals.

Other Embodiments

From the above description, one skilled in the art can easily ascertain the essential characteristics of the present invention, and without departing from the spirit and scope thereof, can make various changes and modifications of the invention to adapt it to various usages and conditions. Thus, other embodiments are also within the claims.

WHAT IS CLAIMED IS:

1. A compound of the following formula:



wherein

R^1 is $-X^1-Y^1-X^2-R^a-X^3-Y^2-X^4-R^b$; and R^2 is $-X^5-Y^3-X^6-R^c-X^7-Y^4-X^8-R^d$; in which each of X^1, X^2, X^3, X^4, X^5, X^6, X^7, and X^8, independently, is a bond, or a C_{1-6} alkylene chain optionally containing a double bond or a triple bond and further optionally substituted with alkyl, alkenyl, alkynyl, alkoxy, hydroxyl, halo, carboxyl, amino, nitro, cyano, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, aminosulfonyl, alkylsulfonylamino, alkylcarbonyloxy, alkyloxycarbonyl, alkylcarbonyl, formyl, alkylcarbonylamino, or aminocarbonyl; each of Y^1, Y^2, Y^3, and Y^4, independently, is a bond, -O-, -S-, -SO-, $-SO_2-$, $-N(R^x)-$, -CO-, $-N(R^x)-CO-$, $-CO-N(R^x)-$, $-N(R^x)-SO_2-$, $-SO_2-N(R^x)-$, $-N(R^x)-CO-O-$, $-O-CO-N(R^x)-$, $-N(R^x)-CO-N(R^y)-$, -O-CO-, -CO-O-, $-O-SO_2-$, or $-SO_2-O-$ where each of R^x and R^y, independently, is hydrogen, alkyl, hydroxylalkyl, amino, cyano, haloalkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, aralkyl, or heteroaralkyl; each of R^a and R^c, independently, is a bond, or cycloalkyl, heterocycloalkyl, cycloalkenyl, heterocycloalkenyl, aryl, or heteroaryl, optionally substituted with alkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, alkoxy, hydroxyl, hydroxylalkyl, carboxyl, halo, haloalkyl, amino, aminoalkyl, nitro, cyano, aryloxy, heteroaryloxy, aralkoxy, heteroaralkoxy, alkylcarbonyloxy, alkyloxycarbonyl, arylcarbonyloxyalkyl, aryloxycarbonylalkyl, alkylcarbonyl, formyl, aminocarbonyl, alkylcarbonylamino, alkylsulfonylamino, aminosulfonyl, aminocarbonyloxy, or alkyloxycarbonylamino; and each of R^b and R^d,

independently, is hydrogen or a cyclic moiety having 3-20 ring atoms, optionally substituted with alkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, alkoxy, hydroxyl, hydroxylalkyl, carboxyl, halo, haloalkyl, amino, aminoalkyl, nitro, cyano, aryloxy, heteroaryloxy, aralkoxy, heteroaralkoxy, alkylcarbonyloxy, alkyloxycarbonyl, arylcarbonyloxyalkyl, aryloxycarbonylalkyl, alkylcarbonyl, formyl, oxo, aminocarbonyl, alkylcarbonylamino, alkylsulfonylamino, aminosulfonyl, aminocarbonyloxy, or alkyloxycarbonylamino;

each of R^3 and R^4, independently, is hydrogen, alkyl, alkoxy, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, alkylcarbonyloxy, alkyloxycarbonyl, alkylcarbonyl, alkylcarbonylamino, or alkylaminocarbonyl; and

A is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, cycloalkenyl, heterocycloalkenyl, aryl, heteroaryl, aralkyl, heteroaralkyl, alkoxy, hydroxyl, hydroxylalkyl, thio, carboxyl, halo, haloalkyl, amino, aminoalkyl, alkylcarbonyloxy, alkyloxycarbonyl, alkylcarbonyl, alkylcarbonylamino, aminocarbonyl, alkylsulfonylamino, aminoisulfonyl, sulfonic acid, or alkylsulfonyl;

provided that neither R^1 nor R^2 is a hydrogen and further provided that at least one of R^1 and R^2 contains a cyclic moiety having 3 to 20 ring atoms or a straight chain having 4 to 24 chain atoms.

2. The compound of claim 1, wherein each of X^1, X^2, X^3, and X^4, independently, is a bond or a C_{1-4} alkylene chain optionally containing a double bond, R^a is a bond, aryl, or heteroaryl; each of Y^1 and Y^2, independently, is a bond, -O-, -S-, $-SO_2-$, $-N(R^x)-$, $-N(R^x)-CO-$, $-N(R^x)-SO_2-$, $-N(R^x)-CO-N(R^y)-$, -O-CO-, -CO-O-, $-O-SO_2-$, or $-SO_2-O-$; and R^b is hydrogen, aryl, or heteroaryl, optionally substituted with alkyl, alkoxy, halo, amino, or cyano.

3. The compound of claim 2, wherein each of X^1, X^2, Y^1, and R^a, independently, is a bond; and Y^2 is a bond, -O-, -CO-O-, or $-N(R^x)-$ where R^x is hydrogen.

4. The compound of claim 1, wherein each of X^5, X^6, X^7, and X^8, independently, is a bond or a C_{1-4} alkylene chain; R^c is a bond, aryl, heteroaryl, or heterocycloalkyl; each of Y^1 and Y^2, independently, is a bond, -O-, -S-, $-SO_2-$, $-N(R^x)-$, $-N(R^x)-CO-$, $-N(R^x)-SO_2-$, $-N(R^x)-CO-N(R^y)-$, -O-CO-, -CO-O-, $-O-SO_2-$, or $-SO_2-O-$; and R^d is hydrogen or a cyclic moiety having 6-15 ring atoms, optionally substituted with alkyl, alkoxy, halo, haloalkyl, or amino.

5. The compound of claim 4, wherein R^c is a bond.

6. The compound of claim 5, wherein Y^3 is -O-, -S-, or $-N(R^x)-$; Y^4 is -O-, -S-, $-N(R^x)-$, $-N(R^x)-CO-$, $-N(R^x)-SO_2-$, or $-N(R^x)-CO-N(R^y)-$; and R^d is phenyl, naphthyl, dihydro-dibenzoazepine, or dibenzocyclo-heptenyl.

7. The compound of claim 5, wherein each of X^5, X^6, X^7, and X^8, independently, is a bond or a C_{1-4} alkylene chain optionally containing a double bond; Y^3 is a bond; Y^4 is -O-, -S-, $-N(R^x)-$, $-N(R^x)-CO-$, $-N(R^x)-SO_2-$, or $-N(R^x)-CO-N(R^y)-$; and R^d is phenyl, naphthyl, dihydro-dibenzoazepine, or dibenzocycloheptenyl.

8. The compound of claim 5, wherein each of Y^3 and Y^4, independently, is a bond, and R^d is hydrogen.

9. The compound of claim 4, wherein R^c is aryl.

10. The compound of claim 9, wherein R^c is phenyl; Y^3 is a bond; Y^4 is -O-, $-N(R^x)-CO-$, $-N(R^x)-SO_2-$, or $-N(R^x)-CO-N(R^y)-$; and R^d is phenyl, naphthyl, dihydro-dibenzoazepine, or dibenzocyclo-heptenyl.

11. The compound of claim 4, wherein R^c is heteroaryl or heterocycloalkyl.

12. The compound of claim 11, wherein R^c is imidazolyl, piperidinyl, or piperazinyl; Y^3 is a bond; Y^4 is a bond, -O-, $-N(R^x)-CO-$, $-N(R^x)-SO_2-$, or -

$N(R^x)$-CO-$N(R^y)$-; and R^d is phenyl, naphthyl, dihydro-dibenzoazepine, or dibenzocycloheptenyl.

13. The compound of claim 1, wherein each of R^3 and R^4, independently, is hydrogen.

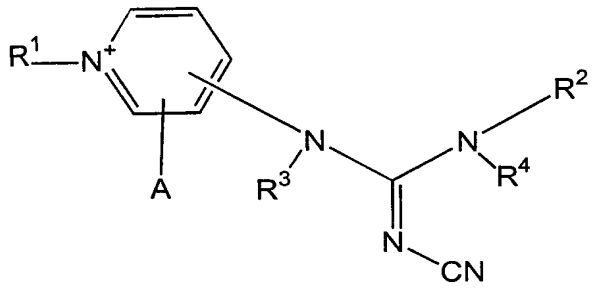
14. The compound of claim 1, wherein A is hydrogen, alkyl, alkoxy, halo, haloalkyl, hydroxyl, hydroxylalkyl, or amino.

15. The compound of claim 1, provided that at least one of R^1 and R^2 contains a cyclic moiety having 5 to 18 ring atoms or a straight chain having 6 to 24 chain atoms.

16. The compound of claim 15, provided that at least one of R^1 and R^2 contains a cyclic moiety having 6 to 14 ring atoms or a straight chain having 7 to 20 chain atoms.

17. The compound of claim 1, where the compound is 4-(*N*'-(6-(4-chloro-phenoxy)-hexyl)-*N*''-cyano-guanidino)-1-methyl-pyridinium, iodide; *N*-(6-(4-chloro-phenoxy)-hexyl)-*N*'-)1-(2-hydroxy-ethyl)-pyridin-4-yl)-*N*''-cyano-guanidine; or 4-(*N*-(4-(5-dimethylamino-naphthalene-1-sulfonylamino)-benzyl)-*N*'-cyano-carbamimidoylmethyl)-1-methyl-pyridinium iodide.

18. A compound of the following formula:



wherein

R^1 is $-X^1-Y^1-X^2-R^a-X^3-Y^2-X^4-R^b$; and R^2 is $-X^5-Y^3-X^6-R^c-X^7-Y^4-X^8-R^d$; in which each of X^1, X^2, X^3, X^4, X^5, X^6, X^7, and X^8, independently, is a bond, or a C_{1-6}

alkylene chain optionally containing a double bond or a triple bond and further optionally substituted with alkyl, alkenyl, alkynyl, alkoxy, hydroxyl, halo, carboxyl, amino, nitro, cyano, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, aminosulfonyl, alkylsulfonylamino, alkylcarbonyloxy, alkyloxycarbonyl, alkylcarbonyl, formyl, alkylcarbonylamino, or aminocarbonyl; each of Y^1, Y^2, Y^3, and Y^4, independently, is a bond, -O-, -S-, -SO-, $-SO_2-$, $-N(R^x)-$, -CO-, $-N(R^x)-CO-$, $-CO-N(R^x)-$, $-N(R^x)-SO_2-$, $-SO_2-N(R^x)-$, $-N(R^x)-CO-O-$, $-O-CO-N(R^x)-$, $-N(R^x)-CO-N(R^y)-$, -O-CO-, -CO-O-, $-O-SO_2-$, or $-SO_2-O-$ where each of R^x and R^y, independently, is hydrogen, alkyl, hydroxylalkyl, amino, cyano, haloalkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, aralkyl, or heteroaralkyl; each of R^a and R^c, independently, is a bond, or cycloalkyl, heterocycloalkyl, cycloalkenyl, heterocycloalkenyl, aryl, or heteroaryl, optionally substituted with alkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, alkoxy, hydroxyl, hydroxylalkyl, carboxyl, halo, haloalkyl, amino, aminoalkyl, nitro, cyano, aryloxy, heteroaryloxy, aralkoxy, heteroaralkoxy, alkylcarbonyloxy, alkyloxycarbonyl, arylcarbonyloxyalkyl, aryloxycarbonylalkyl, alkylcarbonyl, formyl, aminocarbonyl, alkylcarbonylamino, alkylsulfonylamino, aminosulfonyl, aminocarbonyloxy, or alkyloxycarbonylamino; and each of R^b and R^d, independently, is hydrogen or a cyclic moiety having 3-20 ring atoms, optionally substituted with alkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, alkoxy, hydroxyl, hydroxylalkyl, carboxyl, halo, haloalkyl, amino, aminoalkyl, nitro, cyano, aryloxy, heteroaryloxy, aralkoxy, heteroaralkoxy, alkylcarbonyloxy, alkyloxycarbonyl, arylcarbonyloxyalkyl, aryloxycarbonylalkyl, alkylcarbonyl, formyl, oxo, aminocarbonyl, alkylcarbonylamino, alkylsulfonylamino, aminosulfonyl, aminocarbonyloxy, or alkyloxycarbonylamino;

R^3 is hydrogen, alkyl, alkoxy, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, alkylcarbonyloxy, alkyloxycarbonyl, alkylcarbonyl, alkylcarbonylamino, or alkylaminocarbonyl;

R^4 is a C_{1-4} alkylene chain in which the terminal carbon atom not bonded to the guanidinyl nitrogen atom is bonded to a carbon chain atom of X^5 or X^6, or a nitrogen chain atom of Y^3, thereby forming a ring which is optionally substituted with alkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, alkoxy, hydroxyl, hydroxylalkyl, carboxyl, halo, haloalkyl, amino, aminoalkyl,

nitro, cyano, aryloxy, heteroaryloxy, aralkoxy, heteroaralkoxy, alkylcarbonyloxy, alkyloxycarbonyl, arylcarbonyloxyalkyl, aryloxycarbonylalkyl, alkylcarbonyl, formyl, oxo, aminocarbonyl, alkylcarbonylamino, alkylsulfonylamino, aminosulfonyl, aminocarbonyloxy, or alkyloxycarbonylamino;

A is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, cycloalkenyl, heterocycloalkenyl, aryl, heteroaryl, aralkyl, heteroaralkyl, alkoxy, hydroxyl, hydroxylalkyl, thio, carboxyl, halo, haloalkyl, amino, aminoalkyl, alkylcarbonyloxy, alkyloxycarbonyl, alkylcarbonyl, alkylcarbonylamino, aminocarbonyl, alkylsulfonylamino, aminoisulfonyl, sulfonic acid, or alkylsulfonyl;

provided that neither R^1 nor R^2 is a hydrogen and further provided that at least one of R^1 and R^2 contains a cyclic moiety having 3 to 20 ring atoms or a straight chain having 4 to 24 chain atoms.

19. The compound of claim 18, wherein each of X^1, X^2, X^3, and X^4, independently, is a bond or a C_{1-4} alkylene chain optionally containing a double bond; R^a is a bond, aryl, or heteroaryl; each of Y^1 and Y^2, independently, is a bond, -O-, -S-, -SO_2-, -N(R^x)-, -N(R^x)-CO-, -N(R^x)-SO_2-, -N(R^x)-CO-N(R^y)-, -O-CO-, -CO-O-, -O-SO_2-, or -SO_2-O-; and R^b is hydrogen, aryl, or heteroaryl, optionally substituted with alkyl, alkoxy, halo, amino, or cyano.

20. The compound of claim 19, wherein each of X^1, X^2, Y^1, and R^a, independently, is a bond; and Y^2 is a bond, -O-, -CO-O-, or -N(R^x)- where R^x is hydrogen.

21. The compound of claim 18, wherein R^4 and X^5 together form a piperidine ring.

22. The compound of claim 21, wherein each of Y^3, X^6, and R^c, independently, is a bond; each of X^7 and X^8, independently, is a bond or a C_{1-4} alkylene chain optionally substituted with aryl, heteroaryl, aralkyl, or heteroaralkyl; Y^4 is a bond, -O-, -S-, $-SO_2-$, $-N(R^x)-$,$-N(R^x)-CO-$, $-N(R^x)-SO_2-$, $-N(R^x)-CO-N(R^y)-$, -O-CO-, -CO-O-, $-O-SO_2-$, or $-SO_2-O-$; and R^d is hydrogen or a cyclic moiety having 6-15 ring atoms, optionally substituted with alkyl, alkoxy, halo, haloalkyl, or amino.

23. The compound of claim 22, wherein R^d is hydrogen, phenyl, naphthyl, dihydro-dibenzoazepine, or dibenzocyclo-heptenyl, optionally substituted with alkyl, alkoxy, amino, or halo.

24. The compound of claim 23, wherein each of X^1, X^2, Y^1, and R^a, independently, is a bond; each of X^3 and X^4, independently, is a bond or a C_{1-4} alkylene chain optionally containing a double bond; Y^2 is a bond, -O-, -CO-O-, or $-N(R^x)-$ where R^x is hydrogen; and each of R^3 and A, independently, is hydrogen.

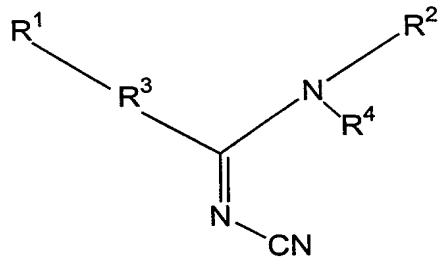
25. The compound of claim 18, wherein A is hydrogen, alkyl, alkoxy, halo, haloalkyl, hydroxyl, hydroxylalkyl, or amino.

26. The compound of claim 18, wherein A is hydrogen.

27. The compound of claim 18, provided that at least one of R^1 and R^2 contains a cyclic moiety having 5 to 18 ring atoms or a straight chain having 6 to 24 chain atoms.

28. The compound of claim 18, provided that at least one of R^1 and R^2 contains a cyclic moiety having 6 to 14 ring atoms or a straight chain having 7 to 20 chain atoms.

29. A compound of the following formula:

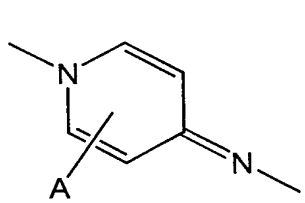


wherein

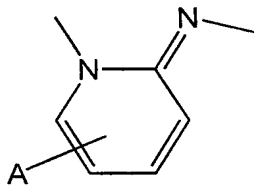
R^1 is $-X^1-Y^1-X^2-R^a-X^3-Y^2-X^4-R^b$; and R^2 is $-X^5-Y^3-X^6-R^c-X^7-Y^4-X^8-R^d$; in which each of X^1, X^2, X^3, X^4, X^5, X^6, X^7, and X^8, independently, is a bond, or a C_{1-6} alkylene chain optionally containing a double bond or a triple bond and further optionally substituted with alkyl, alkenyl, alkynyl, alkoxy, hydroxyl, halo, carboxyl, amino, nitro, cyano, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, aminosulfonyl, alkylsulfonylamino, alkylcarbonyloxy, alkyloxycarbonyl, alkylcarbonyl, formyl, alkylcarbonylamino, or aminocarbonyl; each of Y^1, Y^2, Y^3, and Y^4, independently, is a bond, -O-, -S-, -SO-, $-SO_2-$, $-N(R^x)-$, -CO-, $-N(R^x)-CO-$, $-CO-N(R^x)-$, $-N(R^x)-SO_2-$, $-SO_2-N(R^x)-$, $-N(R^x)-CO-O-$, $-O-CO-N(R^x)-$, $-N(R^x)-CO-N(R^y)-$, -O-CO-, -CO-O-, $-O-SO_2-$, or $-SO_2-O-$ where each of R^x and R^y, independently, is hydrogen, alkyl, hydroxylalkyl, amino, cyano, haloalkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, aralkyl, or heteroaralkyl; each of R^a and R^c, independently, is a bond, or cycloalkyl, heterocycloalkyl, cycloalkenyl, heterocycloalkenyl, aryl, or heteroaryl, optionally substituted with alkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, alkoxy, hydroxyl, hydroxylalkyl, carboxyl, halo, haloalkyl, amino, aminoalkyl, nitro, cyano, aryloxy, heteroaryloxy, aralkoxy, heteroaralkoxy, alkylcarbonyloxy, alkyloxycarbonyl, arylcarbonyloxyalkyl, aryloxycarbonylalkyl, alkylcarbonyl, formyl, aminocarbonyl, alkylcarbonylamino, alkylsulfonylamino, aminosulfonyl, aminocarbonyloxy, or alkyloxycarbonylamino; and each of R^b and R^d, independently, is hydrogen or a cyclic moiety having 3-20 ring atoms, optionally substituted with alkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, alkoxy, hydroxyl, hydroxylalkyl, carboxyl, halo, haloalkyl, amino, aminoalkyl, nitro, cyano, aryloxy, heteroaryloxy, aralkoxy, heteroaralkoxy, alkylcarbonyloxy, alkyloxycarbonyl, arylcarbonyloxyalkyl, aryloxycarbonylalkyl, alkylcarbonyl, formyl, oxo, aminocarbonyl,

alkylcarbonylamino, alkylsulfonylamino, aminosulfonyl, aminocarbonyloxy, or alkyloxycarbonylamino;

R^3 is



or



where the pyridine ring is bonded to R^1 and A is H, alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, cycloalkenyl, heterocycloalkenyl, aryl, heteroaryl, aralkyl, heteroaralkyl, alkoxy, hydroxyl, hydroxylalkyl, thio, carboxyl, halo, haloalkyl, amino, aminoalkyl, alkylcarbonyloxy, alkyloxycarbonyl, alkylcarbonyl, alkylcarbonylamino, aminocarbonyl, alkylsulfonylamino, aminoisulfonyl, sulfonic acid, or alkylsulfonyl; and

R^4 is H, alkyl, alkoxy, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, alkylcarbonyloxy, alkyloxycarbonyl, alkylcarbonyl, alkylcarbonylamino, or alkylaminocarbonyl;

provided that neither R^1 nor R^2 is a hydrogen and further provided that at least one of R^1 and R^2 contains a cyclic moiety having 3 to 20 ring atoms or a straight chain having 4 to 24 chain atoms; or a salt thereof.

30. The compound of claim 29, wherein each of X^1, X^2, X^3, and X^4, independently, is a bond or a C_{1-4} alkylene chain optionally containing a double bond; R^a is a bond, aryl, or heteroaryl; each of Y^1 and Y^2, independently, is a bond, -O-, -S-, $-SO_2-$, $-N(R^x)-$, $-N(R^x)-CO-$, $-N(R^x)-SO_2-$, $-N(R^x)-CO-N(R^y)-$, -O-CO-, -CO-O-, $-O-SO_2-$, or $-SO_2-O-$; and R^b is hydrogen, aryl, or heteroaryl, optionally substituted with alkyl, alkoxy, halo, amino, or cyano.

31. The compound of claim 30, wherein each of X^1, X^2, Y^1, and R^a, independently, is a bond; and Y^2 is a bond, -O-, -CO-O-, or $-N(R^x)-$ where R^x is hydrogen.

32. The compound of claim 29, wherein each of X^5, X^6, X^7, and X^8, independently, is a bond 32or a C_{1-4} alkylene chain; R^c is a bond, aryl, heteroaryl, or heterocycloalkyl; each of Y^1 and Y^2, independently, is a bond, -O-, -S-, $-SO_2-$, $-N(R^x)-$, $-N(R^x)-CO-$, $-N(R^x)-SO_2-$, $-N(R^x)-CO-N(R^y)-$, -O-CO-, -CO-O-, -O-SO_2-, or $-SO_2-O-$; and R^d is hydrogen or a cyclic moiety having 6-15 ring atoms, optionally substituted with alkyl, alkoxy, halo, haloalkyl, or amino.

33. The compound of claim 32, wherein R^c is a bond.

34. The compound of claim 33, wherein Y^3 is -O-, -S-, or $-N(R^x)-$; Y^4 is -O-, -S-, $-N(R^x)-$, $-N(R^x)-CO-$, $-N(R^x)-SO_2-$, or $-N(R^x)-CO-N(R^y)-$; and R^d is phenyl, naphthyl, dihydro-dibenzoazepine, or dibenzocyclo-heptenyl.

35. The compound of claim 33, wherein Y^3 is a bond; Y^4 is -O-, -S-, $-N(R^x)-$, $-N(R^x)-CO-$, $-N(R^x)-SO_2-$, or $-N(R^x)-CO-N(R^y)-$; and R^d is phenyl, naphthyl, dihydro-dibenzoazepine, or dibenzocyclo-heptenyl.

36. The compound of claim 33, wherein each of Y^3 and Y^4, independently, is a bond, and R^d is hydrogen.

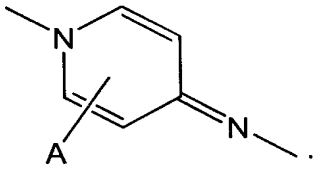
37. The compound of claim 32, wherein R^c is aryl.

38. The compound of claim 37, wherein R^c is phenyl; Y^3 is a bond; Y^4 is -O-, $-N(R^x)-CO-$, $-N(R^x)-SO_2-$, or $-N(R^x)-CO-N(R^y)-$; and R^d is phenyl, naphthyl, dihydro-dibenzoazepine, or dibenzocyclo-heptenyl.

39. The compound of claim 32, wherein R^c is heteroaryl or heterocycloalkyl.

40. The compound of claim 39, wherein R^c is imidazolyl, piperidinyl, or piperazinyl; Y^3 is a bond; Y^4 is a bond, -O-, $-N(R^x)-CO-$, $-N(R^x)-SO_2-$, or $-N(R^x)-CO-N(R^y)-$; and R^d is phenyl, naphthyl, dihydro-dibenzoazepine, or dibenzocycloheptenyl.

41. The compound of claim 29, wherein R^3 is



42. The compound of claim 29, wherein A is H, alkyl, alkoxy, halo, haloalkyl, hydroxyl, hydroxylalkyl, or amino.

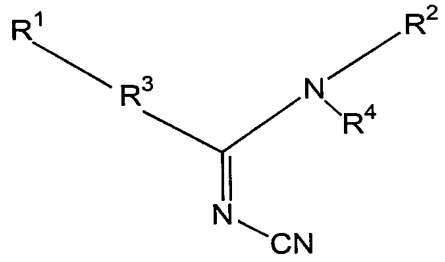
43. The compound of claim 29, wherei R^4 is H.

44. The compound of claim 29, provided that at least one of R^1 and R^2 contains a cyclic moiety having 5 to 18 ring atoms or a straight chain having 6 to 24 chain atoms.

45. The compound of claim 44, provided that at least one of R^1 and R^2 contains a cyclic moiety having 6 to 14 ring atoms or a straight chain having 7 to 20 chain atoms.

46. The compound of claim 29, where the compound is 5-dimethylamino-naphthalene-1-sulfonic acid (4-(*N*'-cyano-*N*"-(1-methyl-1*H*-pyridin-4-ylidene)-guanidinomethyl)-phenyl)-amide; *N*-(6-(4-chloro-phenoxy)-hexyl)-*N*'-cyano-*N*"-(1-methyl-1*H*-pyridin-4-ylidene)-guanidine; or *N*-(6-(4-chloro-phenoxy)-hexyl)-*N*'-(1-(2-hydroxy-ethyl)-1*H*-pyridin-4-ylidene)-*N*"-cyano-guanidine.

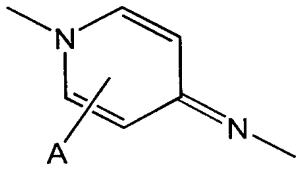
47. A compound of the following formula:



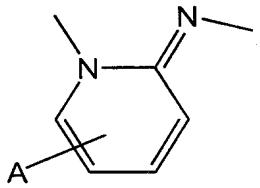
wherein

R^1 is $-X^1-Y^1-X^2-R^a-X^3-Y^2-X^4-R^b$; and R^2 is $-X^5-Y^3-X^6-R^c-X^7-Y^4-X^8-R^d$; in which each of X^1, X^2, X^3, X^4, X^5, X^6, X^7, and X^8, independently, is a bond, or a C_{1-6} alkylene chain optionally containing a double bond or a triple bond and further optionally substituted with alkyl, alkenyl, alkynyl, alkoxy, hydroxyl, halo, carboxyl, amino, nitro, cyano, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, aminosulfonyl, alkylsulfonylamino, alkylcarbonyloxy, alkyloxycarbonyl, alkylcarbonyl, formyl, alkylcarbonylamino, or aminocarbonyl; each of Y^1, Y^2, Y^3, and Y^4, independently, is a bond, -O-, -S-, -SO-, $-SO_2-$, $-N(R^x)-$, -CO-, $-N(R^x)-CO-$, $-CO-N(R^x)-$, $-N(R^x)-SO_2-$, $-SO_2-N(R^x)-$, $-N(R^x)-CO-O-$, $-O-CO-N(R^x)-$, $-N(R^x)-CO-N(R^y)-$, -O-CO-, -CO-O-, $-O-SO_2-$, or $-SO_2-O-$ where each of R^x and R^y, independently, is hydrogen, alkyl, hydroxylalkyl, amino, cyano, haloalkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, aralkyl, or heteroaralkyl; each of R^a and R^c, independently, is a bond, or cycloalkyl, heterocycloalkyl, cycloalkenyl, heterocycloalkenyl, aryl, or heteroaryl, optionally substituted with alkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, alkoxy, hydroxyl, hydroxylalkyl, carboxyl, halo, haloalkyl, amino, aminoalkyl, nitro, cyano, aryloxy, heteroaryloxy, aralkoxy, heteroaralkoxy, alkylcarbonyloxy, alkyloxycarbonyl, arylcarbonyloxyalkyl, aryloxycarbonylalkyl, alkylcarbonyl, formyl, aminocarbonyl, alkylcarbonylamino, alkylsulfonylamino, aminosulfonyl, aminocarbonyloxy, or alkyloxycarbonylamino; and each of R^b and R^d, independently, is hydrogen or a cyclic moiety having 3-20 ring atoms, optionally substituted with alkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, alkoxy, hydroxyl, hydroxylalkyl, carboxyl, halo, haloalkyl, amino, aminoalkyl, nitro, cyano, aryloxy, heteroaryloxy, aralkoxy, heteroaralkoxy, alkylcarbonyloxy, alkyloxycarbonyl, arylcarbonyloxyalkyl, aryloxycarbonylalkyl, alkylcarbonyl, formyl, oxo, aminocarbonyl, alkylcarbonylamino, alkylsulfonylamino, aminosulfonyl, aminocarbonyloxy, or alkyloxycarbonylamino;

R^3 is



or



where the pyridine ring is bonded to R^1 and A is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, cycloalkenyl, heterocycloalkenyl, aryl, heteroaryl, aralkyl, heteroaralkyl, alkoxy, hydroxyl, hydroxylalkyl, thio, carboxyl, halo, haloalkyl, amino, aminoalkyl, alkylcarbonyloxy, alkyloxycarbonyl, alkylcarbonyl, alkylcarbonylamino, aminocarbonyl, alkylsulfonylamino, aminoisulfonyl, sulfonic acid, or alkylsulfonyl; and

R^4 is a C_{1-4} alkylene chain in which the terminal carbon atom not bonded to the guanidinyl nitrogen atom is bonded to a carbon chain atom of X^5 or X^6, or a nitrogen chain atom of Y^3, thereby forming a ring which is optionally substituted with alkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, alkoxy, hydroxyl, hydroxylalkyl, carboxyl, halo, haloalkyl, amino, aminoalkyl, nitro, cyano, aryloxy, heteroaryloxy, aralkoxy, heteroaralkoxy, alkylcarbonyloxy, alkyloxycarbonyl, arylcarbonyloxyalkyl, aryloxycarbonylalkyl, alkylcarbonyl, formyl, oxo, aminocarbonyl, alkylcarbonylamino, alkylsulfonylamino, aminosulfonyl, aminocarbonyloxy, or alkyloxycarbonylamino;

provided that neither R^1 nor R^2 is a hydrogen and further provided that at least one of R^1 and R^2 contains a cyclic moiety having 3 to 20 ring atoms or a straight chain having 4 to 24 chain atoms, or a salt thereof.

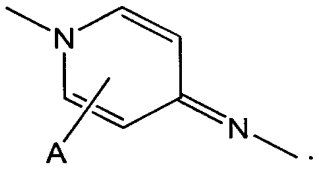
48. The compound of claim 47, wherein each of X^1, X^2, X^3, and X^4, independently, is a bond or a C_{1-4} alkylene chain optionally containing a double bond; R^a is a bond, aryl, or heteroaryl; each of Y^1 and Y^2, independently, is a bond, -O-, -S-, $-SO_2-$, $-N(R^x)-$, $-N(R^x)-CO-$, $-N(R^x)-SO_2-$, $-N(R^x)-CO-N(R^y)-$, -O-CO-, -CO-O-, $-O-SO_2-$, or $-SO_2-O-$; and R^b is hydrogen, aryl, or heteroaryl, optionally substituted with alkyl, alkoxy, halo, amino, or cyano.

49. The compound of claim 47, wherein R^4 and X^5 together form a piperidine ring.

50. The compound of claim 49, wherein each of Y^3, X^6, and R^c, independently, is a bond; each of X^7 and X^8, independently, is a bond or a C_{1-4} alkylene chain optionally containing a double bond and further optionally substituted with aryl, heteroaryl, aralkyl, or heteroaralkyl; Y^4 is a bond, -O-, -S-, -SO_2-, -$N(R^x)$-, -$N(R^x)$-CO-, -$N(R^x)$-SO_2-, -$N(R^x)$-CO-$N(R^y)$-, -O-CO-, -CO-O-, -O-SO_2-, or -SO_2-O-; and R^d is hydrogen or a cyclic moiety having 6-15 ring atoms, optionally substituted with alkyl, alkoxy, halo, haloalkyl, or amino.

51. The compound of claim 50, wherein R^d is hydrogen, phenyl, naphthyl, dihydro-dibenzoazepine, or dibenzocyclo-heptenyl, optionally substituted with alkyl, alkoxy, amino, or halo.

52. The compound of claim 47, wherein R^3 is



53. The compound of claim 47, wherein A is H, alkyl, alkoxy, halo, haloalkyl, hydroxyl, hydroxylalkyl, or amino.

54. The compound of claim 47, provided that at least one of R^1 and R^2 contains a cyclic moiety having 5 to 18 ring atoms or a straight chain having 6 to 24 chain atoms.

55. The compound of claim 54, provided that at least one of R^1 and R^2 contains a cyclic moiety having 6 to 14 ring atoms or a straight chain having 7 to 20 chain atoms.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US00/09169

A. CLASSIFICATION OF SUBJECT MATTER
IPC(7) :CO7D 213/02; A61K 31/44
US CL :514/357; 546/306
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/357; 546/306

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

NONE

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS COMPUTER SEARCH 1966-TO DATE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	PETERSEN. Synthesis and hypotensive activity of N-alkyl-N''-cyano-N'-pyridylguanidines. J. Med. Chem. 1978. volume 21, No. 8. pages 773-81.	1-55

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search 16 JUNE 2000	Date of mailing of the international search report 14 JUL 2000
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer ZINNA N. DAVIS Telephone No. (703) 308-1235

Form PCT/ISA/210 (second sheet)(July 1992)★